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Original Communications

SULFATHIAZOLE IN THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN

A REPORT ON 167 PATIENTS TREATED WITH SULFATHIAZOLE AND A COMPARISON WITH 93 PATIENTS TREATED WITH SULFAPYRIDINE

JOHN P. SCOTT, M.D., PHILADELPHIA, PA., AND
ALBERT M. JONES, M.D., MEMPHIS, TENN.

SULFATHIAZOLE, 2 (para-amido-benzene-sulfonamido-) thiazole, was synthesized by Fosbinder and Walter[1] and by Lott and Bergeim.[2] It was found by VanDyke, Greep, Rake, and McKee[3] to be less toxic than sulfapyridine, to be more rapidly excreted from the body, and to be conjugated to a less extent in the blood. McKee, Rake, Greep and VanDyke[4] found it to be about as effective as sulfapyridine in experimental infections in mice. Reinhold, Flippin and Schwartz[5] studied the drug in adult patients. They found the rectal absorption to be very small. Given intravenously, it was almost quantitatively eliminated in the urine in twenty-four hours. It was quickly absorbed, giving a level of 4.5 mg. per 100 c.c. of blood within one hour of administering a single 3 Gm. dose. Occasionally they found crystals in the urine. They estimated that 84 per cent to 93 per cent was eliminated in the urine in twenty-four hours. On continued administration, a large proportion remained unconjugated. They observed few toxic effects; vomiting was the most common; and there were no effects on the blood. Microscopic hematuria occurred in five of eighty-three patients treated, and dermatitis occurred in three. The dermal effects of sulfathiazole have been discussed by Haviland and Long.[6] Sulfathiazole is very sparingly soluble in water (60 mg. per 100 c.c. water). It can be estimated in the blood by the method of Marshall.[7]

From the Department of Pediatrics, School of Medicine, University of Pennsylvania.

One hundred and fifty-five of the sulfathiazole-treated patients were from the medical services of the Children's Hospital, Philadelphia; 5 patients were from the services of Dr. T. C. Kelly, Dr. R. M. Tyson, and Dr. T. S. Wilder at St. Christopher's Hospital, Philadelphia; 4 were from the pediatric service of the Presbyterian Hospital, Philadelphia; and 3 were from the service of Dr. T. S. Wilder at the Abington Memorial Hospital, Abington, Pa. The authors are indebted to Dr. A. D. Waltz for most of the laboratory determinations and to Dr. R. S. Bromer for most of the x-ray studies.

The sulfathiazole used in this study was supplied through the courtesy of Dr. George A. Harrop, Director of the Squibb Institute for Medical Research, New Brunswick, N. J.

CASES USED IN THE STUDY

A total of 167 cases was studied, of which 146 were thought to be lobar pneumonia; 19, bronchopneumonia; and in 2 the diagnosis was uncertain. The diagnosis of pneumonia was made by the admitting house officer. An attempt was made to ascertain from the history the time of onset of the pulmonary process in order that the duration of the course could be measured. In many instances there was a history of respiratory symptoms of mild grade, followed by the sudden occurrence of high fever, dyspnea, and toxicity. In other cases there was a gradual onset in which the beginning of consolidation could be determined less exactly.

In most of the cases the diagnosis was confirmed and the lesion localized by roentgen studies. In a few cases, in spite of rather definite physical signs, no unmistakable roentgenographic shadows were found.

Two of the patients treated were in extremis when admitted and failed to receive satisfactory doses of the drug. In all the other cases an adequate dosage for twenty-four hours was given, and they were, therefore, included in the series. The patients receiving sulfapyridine were similarly studied.

LABORATORY STUDIES

A complete blood count with a differential count and a urinalysis were done in each case at the time of admission. Before any treatment was started, a sputum culture was obtained, in some cases from a laryngeal swab, and in other cases from a swab passed through the nares into the rhinopharynx. From these swabs a direct smear, typing, and culture were made; no mice were used in the typings. In most cases a blood culture was made.

In 85 cases pneumococci were recovered from the swabs, and of these typing was possible in 42 instances. In 2 cases pneumococci were recovered from the blood culture, one a Type VI, the other not typable.

During therapy blood counts were repeated every two or three days to detect any toxic effects such as hemolytic anemia or granulocytopenia. Urinalyses were repeated frequently, search being made for erythrocytes and sulfathiazole crystals. Blood levels of sulfathiazole were determined in 80 cases. Their importance will be discussed later.

CLINICAL OBSERVATION

The temperature was recorded every four hours. Examinations of the chests were made to detect the accumulation of fluid or migration to new sites in the lungs. The skin was observed in order to detect changes in color and eruptions which might follow the administration of the drug. We did not attempt to say that the pneumonic process was completely resolved at a definite time in any case. The ears were observed frequently, and otitis, catarrhal or suppurative, was noted. X-ray examinations

were repeated in many of the patients, in some cases a number of times. In many cases where fluid was suspected, exploratory thoracentesis was performed.

SULFATHIAZOLE THERAPY

The sulfathiazole was received in the form of tablets, which were usually crushed to a powder and given with milk or fruit juices. The tablets were given whole to some of the older children. The nursing staff experienced little difficulty in giving this drug; they found it no harder to give than other relatively insoluble drugs such as bismuth or acetylsalicylic acid.

The dosage of sulfathiazole was calculated according to weight. In all but a few cases a daily dose of 1 grain (0.065 Gm.) per pound of body weight was used. Usually one-fourth to one-half of this amount was given as an initial dose, and then one-eighth of the daily dose was given every three hours day and night, the patients being awakened if necessary. This was continued until the temperature had been normal for forty-eight hours, or until the physician felt it was no longer necessary. In some cases the individual physicians modified this dosage slightly, and in some cases it was stopped because of fear of toxic effects. In a number of cases in which it was stopped, fever recurred, and the administration of the drug was resumed.

OTHER THERAPY

Where indicated, oxygen therapy was used, either with the oxygen tent, or, in infants, with the Burgess box. Transfusion was used when the physician felt it was indicated. Other forms of therapy such as enemas, measures to combat distention, measures to secure a free nasal airway, incision of eardrums, aural instillations, and sponging were used when indicated.

SULFAPYRIDINE THERAPY

This was conducted similarly to the sulfathiazole therapy except that 58 patients treated between Oct. 1, 1938, and June 1, 1939, received 1½ grains of this drug per pound per day; this drug was used in the fall of 1939 in 35 cases until the supply of sulfathiazole became available. These 35 cases received for the most part 1 grain per pound per day.

RESULTS OF TREATMENT

In nearly every case sulfathiazole seemed to precipitate an early crisis, similar in character to the natural crisis, to that produced by specific serum, and to that produced by sulfapyridine. Usually within twelve hours a change occurred: the fever lessened, the toxicity lessened, dyspnea was relieved, and the patient began to feel better. In many cases fever disappeared permanently in 24 hours. After 48 hours few of the

patients had fever, and after 72 hours only 19 of 158 patients successfully treated had fever. Coincident with the fall in temperature the child's appetite improved, and there was a return of activity and responsiveness to environment. In a few cases listlessness did not disappear until the drug was stopped, in spite of improvement in other respects. Usually physical signs in the lungs improved with the abatement of fever, but great variability was noticed in this clearing, as also it can be noticed after the natural crisis of pneumonia.

COMPLICATIONS

Otitis is a frequent complication of pneumonia, especially in the younger patients. It is our impression that even under expectant treatment this otitis is of less virulence and is less threatening than other forms of otitis, such as that following scarlet fever and streptococcic throat infections. In this series 87 patients had otitis; of these, 56 were catarrhal and resolved without drainage. In 31 cases the otitis was suppurative and responded well to treatment as evidenced by an early return to normal temperature and by the fact that in no instance did mastoiditis develop.

Pleural effusion occurred in 7 patients, one of whom died. These patients are described individually.

CASE 40324.—H. T., colored male, aged 6 weeks, was admitted on Feb. 20, 1940. Death was caused by multiple staphylococcic pulmonary abscesses and empyema. When admitted, he had jaundice, catarrhal otitis, and lobar pneumonia, but no definite pneumonia was found in the x-ray examination. Administration of sulfathiazole was begun immediately, at which time there were 13,800 leucocytes and 68 per cent neutrophiles. Serum bilirubin was 7.1 mg. per 100 c.c. On February 22 the leucocytes had fallen to 2,500 with 8 per cent neutrophiles, and the administration of the drug was stopped. On February 23 the right side of the chest was flat to percussion, and x-rays showed a massive effusion. For some reason this was not recovered by thoracentesis, which was unsuccessful. This infant died on February 23. Necropsy showed multiple abscesses of the right lung and massive empyema, from both of which, as well as the heart blood, *Staphylococcus aureus* was grown.

CASE 40875.—M. S., white female, aged 4 years, was admitted on May 16, 1940. She had Type XXXI pneumonia with empyema yielding *Staphylococcus aureus* on culture. She was admitted with lobar pneumonia; fluid was suspected and its presence was indicated in early films. The throat culture showed Type XXXI pneumococcus. Sulfathiazole was started at once. A dry tap was made on May 19, but on May 20 10 c.c. of pus were withdrawn, from which grew *Staphylococcus aureus hemolyticus*. As the sulfathiazole seemed ineffective, Type XXXI antipneumococcic serum was given. This caused a violent chill, and no more was given. Sulfapyridine was then given for two days; then sulfathiazole was resumed until June 10. The temperature never completed subsided, and on May 27 220 c.c. of pus were aspirated from the chest and on May 29 65 c.c. more. On June 1 thoracotomy was performed, and 1200 c.c. of pus were removed. On July 3, 1940, the child was discharged, completely recovered.

CASE 381088.—W. P., colored male, aged 9 years, was admitted on Feb. 16, 1940. He had Type VI pneumonia with small pleural effusion resolving without thora-

centesis or operation. He was admitted with lobar pneumonia. Throat culture showed Type VI pneumococcus. Sulfathiazole was started immediately. The temperature abated but remained 1 to 2 degrees above normal. Fluid was suspected, and x-ray confirmed this suspicion. Because sulfathiazole was considered ineffective, Type VI antipneumococcic serum was given. A violent reaction ensued, but the temperature fell to a lower level. On March 16 the signs of fluid were still present in the films, but by April 2 they had disappeared.

CASE 39134.—A. D., colored male, aged 21 months, was admitted on Jan. 14, 1940. There was recurrence of pneumonia in this patient who had previously been treated with sulfapyridine, with small effusion recovering without operation. The patient was discharged on Dec. 28, 1939, having had pneumonia treated successfully with sulfapyridine. He was admitted with lobar pneumonia which was confirmed by x-ray. Throat culture showed Type XIV pneumococcus. On admission a pleural line was seen in the films; this was much more marked on January 29, when the next film was made. Sulfathiazole was started at once but after five days with no improvement, it was considered ineffective and sulfapyridine was substituted. The temperature fell promptly to normal and remained normal until January 25. The sulfapyridine had been stopped on January 22 but was resumed. On January 31 2 c.c. of straw-colored fluid were withdrawn from the pleural cavity. This was sterile. The patient was discharged cured on Feb. 17, 1940.

CASE 4093.—C. D., colored female, aged 10, was admitted on Jan. 18, 1940. She had lobar pneumonia with small effusion recovering with sulfathiazole. Diagnosis was confirmed by x-ray. Sputum showed pneumococci which did not type. Sulfathiazole was given from January 18 to January 30, and from February 5 to February 12. Physical and x-ray signs of fluid appeared. Thoracentesis on January 29 yielded 10 c.c. of brownish fluid containing Type IV pneumococcus. Other taps yielded only blood. The process resolved completely, and x-ray was negative for fluid on June 6, 1940.

CASE STX.—T. F., white male, aged 4 years, was admitted on Jan. 25, 1940, to St. Christopher's Hospital. He had lobar pneumonia with small effusion resolving with sulfathiazole and one thoracentesis. X-ray showed marked pleural thickening. A pneumococcus which did not type was found in the throat culture. Sulfathiazole was started immediately. On January 27, 25 c.c. of cloudy fluid were aspirated from the chest. This proved to be sterile. Temperature reached normal on January 29. Administration of the drug was stopped on January 30 when x-ray showed marked clearing of the effusion. The patient was discharged well on February 11.

CASE 40486.—J. D., white male, aged 10 months, was admitted on Mar. 19, 1940. The diagnosis was lobar pneumonia with x-ray evidence of fluid. Pneumonia was found clinically. Sulfathiazole treatment was started at once, and the temperature was normal in 18 hours. On March 26 x-ray showed a small band of pleural exudate although the patient was free of symptoms.

Of these cases, it may be assumed that treatment was successful in the last two, in that prompt control of temperature was secured and operation was avoided. In the first case, the patient died, and multiple staphylococcus abscess formation was found. In the other four, sulfathiazole appeared to be ineffective.

DEATHS

Five of the patients given sulfathiazole died. Two of these patients were admitted in extremis; they received very trifling amounts of the

drug, and it is questionable how much of it they could absorb. Their cases may be summarized as follows:

CASE 4085.—White male, aged 5 months, was admitted on Jan. 16, 1940, with temperature of 106° F. and with questionable physical signs. The plasma carbon dioxide was 18 volumes per cent. The throat culture showed *Staphylococcus aureus*. X-ray did not confirm the pneumonia. Blood cultures taken during life and immediately post mortem showed *Staphylococcus aureus*. The patient died within 24 hours of admission. No necropsy was permitted.

CASE 40757.—I. W., colored male, aged 3 months, was admitted on April 23, 1940, with diagnosis of pneumonia, congenital heart disease, and mongolism. He was given 5 c.c. of 5 per cent sodium sulfathiazole intravenously. This was followed by sulfathiazole by mouth, only 2 grains of which were given before death. Necropsy showed patent interventricular septum and bronchopneumonia.

Two other patients, who received adequate doses of sulfathiazole for at least 24 hours, failed to respond to the drug. Their cases may be summarized as follows:

CASE 40538.—A. G., white female, aged 5 weeks, was admitted on Mar. 30, 1940. She was a Mongolian idiot with lobar pneumonia confirmed by x-ray. Administration of sulfathiazole was started at once. In 36 hours the temperature fell. It was normal until April 3, when a secondary rise to 101° F. occurred. At the time of this rise dyspnea and cyanosis appeared, and the infant died with circulatory failure. Necropsy showed lobar pneumonia and pulmonary edema.

CASE 40285.—C. F., white female, aged 9 months, was admitted Feb. 8, 1940. On admission her temperature was 107° F. A clinical diagnosis of lobar pneumonia was not substantiated in the films, but sputum contained Type XX pneumococci. Sulfathiazole was given for 30 hours after admission; then the patient died. No necropsy was permitted.

The fifth patient who died has been described among the cases developing pleural effusion (CASE 40324, H. T., aged 6 weeks).

DURATION OF FEVER IN THE GROUP

In 158 cases satisfactory results were obtained. Of these patients, the majority had been ill but a short time before treatment was started. The whole group had been ill for a total of 358.5 days, or for an average time of 2.27 days. Of this group 110 had been ill for 48 hours or less; only 33 cases, for 3 or 4 days; and only 15 cases, for 5 days or more.

Between the beginning of treatment and the beginning of a permanent normal temperature, the 158 cases had fever for a total of 285 days, or an average time of 1.80 days. The total course of these treated cases, therefore, averaged 4.07 days. While there was no control group in the season of 1939-1940 with which to compare these patients, there was a group of 46 cases treated expectantly in the season of 1938-1939 in which the total course averaged 7.38 days.

Included in the average time after treatment was begun are a number of cases showing complications. One of the pleural effusion cases previously described returned to normal in 4½ days; the other, in 18 hours. These cases are included in this group of successfully treated cases. Also included are three cases in which we felt that the drug had not been

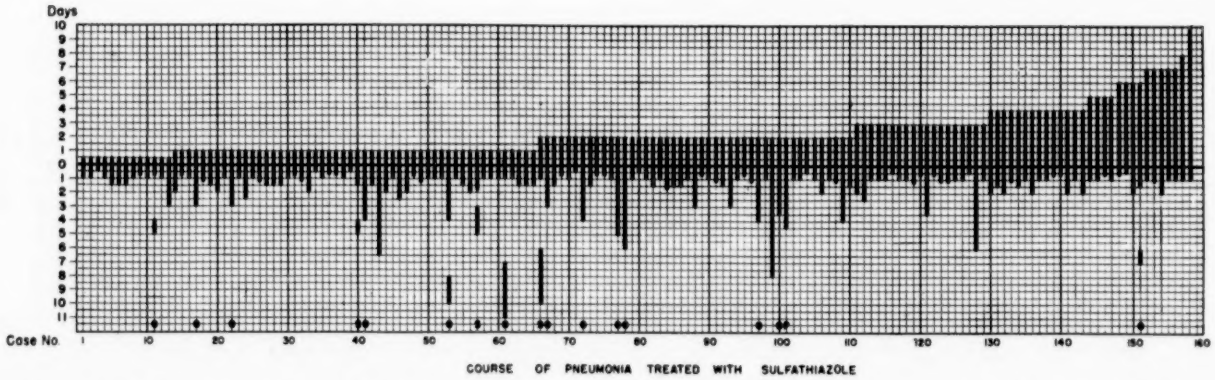


Chart 1.—A graphic representation of the course of pneumonia in 158 successfully treated cases. The zero line represents the time of beginning of treatment with sulfathiazole. The length of the vertical heavy lines above the zero line indicates the length in days of the pneumonic process before treatment was begun. The length of the same lines below the zero line indicates the time in days between the beginning of treatment and the beginning of a permanent normal temperature. Where the line is broken, a recurrence of fever took place. The averages quoted include all these recurrences. The symbols, O, S, and P, near the base line indicate, respectively, Otitis Media, Stopped Administration of Drug Too Soon, and Pleural Effusion.

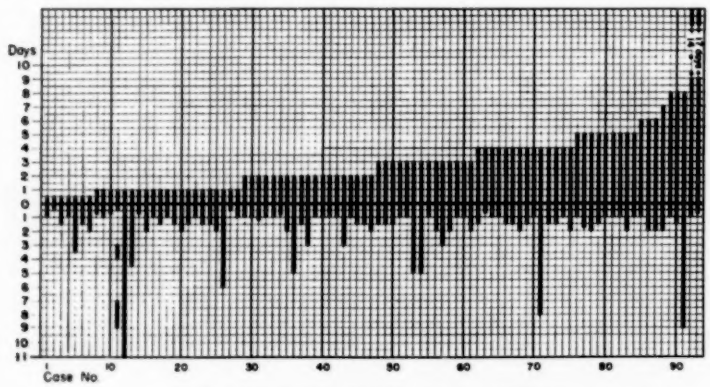
continued long enough; these developed recurrences of fever and averaged in length 6.66 days after starting treatment. In thirteen cases in which otitis media was a complication, the average duration of fever was 6 days.

Of the 158 successfully treated patients, 81 reached normal in 24 hours; 49, in 48 hours; and 9, in 72 hours. The remaining 19 patients required more than 72 hours to become normal. In only 5 of this group of 19 were complications absent.

In the natural course of pneumonia treated expectantly, one would expect the upper and lower margins of the vertical lines in the graph to be almost parallel; that is, the longer the illness had lasted before treatments, the sooner crisis would be expected. In this graph it will be seen that there is no relation between these two parts of the course, and that control of temperature almost paralleled the zero line or the administration of sulfathiazole.

RESULTS IN BRONCHOPNEUMONIA

In 18 cases the diagnosis of bronchopneumonia was made and confirmed in x-ray films. These cases were similar to the group as a whole in their duration before treatment was begun, averaging 2.1 days of illness, compared to 2.27 days for the entire group. Their response to treatment was also similar to that of the group as a whole, their course after treatment lasting an average of 1.62 days, compared to 1.80 days for the whole group.



COURSE OF PNEUMONIA TREATED WITH SULFAPYRIDINE

Chart 2.—A graphic representation of the course of pneumonia in ninty-three patients treated with sulfapyridine. The length of the heavy vertical lines above the zero line indicates the number of days of illness before treatment was begun; the length of the same lines below the zero line indicates the number of days between the time treatment was begun and the beginning of a permanent normal temperature. Where the line is broken, a fever recurred.

COMPARISON WITH SULFAPYRIDINE

During the early part of the 1939-1940 pneumonia season, before the supply of sulfathiazole became ample, 35 cases were treated with sulfa-

pyridine, used in a similar manner to that in which the sulfathiazole was used. To these have been added 58 cases reported by one of us, (J. P. S.),[8] which were treated during the pneumonia season of 1938-1939. These cases were similar clinically and in the duration of the illness when treatment was begun. The 1938-1939 cases had a duration of 2.94 days before treatment and a duration of 2.00 days after treatment; the 1939-1940 cases had a duration of 3.28 days before treatment and a duration of 1.55 days after treatment. The total of these cases is graphically represented in Chart 2 in a manner similar to that in which the sulfathiazole cases are represented. The 1939-1940 series contained one long case lasting 11 days, believed to be caused by stopping the administration of the drug too soon.

There was some feeling among the attending physicians that sulfapyridine was capable of producing a more prompt fall of temperature than was sulfathiazole. A comparison of the times elapsing between the first dose of the drugs and the first significant fall of temperature is shown in Table I.

TABLE I

CASES IN WHICH CRITICAL FALL BEGAN IN	SULFAPYRIDINE	SULFATHIAZOLE
12 hours	25 or 71.4%	104 or 65.8%
24 hours	7 or 20%	43 or 27.2%
26 hours	3 or 8.6%	8 or 5.0%
More than 36 hours	0	3 or 1.9%

One cannot infer from these inadequate figures that there is any superiority of one drug over the other in this respect. Further study of a greater amount of material is necessary to make any positive conclusions in this matter.

THE SULFATHIAZOLE LEVEL

The blood sulfathiazole level was determined in 80 cases, usually taken after two days of administration of the drug. In an attempt to determine the value of these determinations, the levels are classified and compared in Table II.

TABLE II

LEVEL IN BLOOD PER 100 C.C. (MG.)	NO. OF CASES	AVER. DURATION OF ELEVATED TEMPERATURE (DAYS)
Between 1-2	6	1.25
2-3	23	2.1
3-4	23	1.4
4-5	19	1.4
5-6	5	1.7
6-7	1	0.75
7-8	2	2.00
8-9	1	2.00

It was impossible to infer anything from these levels, and it is felt that it is only important to measure them when the drug seems ineffective.

TOXIC EFFECTS

In a previous paper by one of us, already quoted,[8] few toxic effects were observed when moderate doses of sulfapyridine were used for a total of 96 hours. Of these, vomiting was the commonest, although withdrawal of the drug was necessary in only 2 of 58 cases. Using a similar dose of sulfathiazole, vomiting occurred in 21 cases of a total of 164, or 12.5 per cent, but it was not serious enough to necessitate withdrawal of the drug in any case. Diarrhea occurred three times in this series; it seemed very certainly to be caused by the drug, but likewise was not severe enough to warrant discontinuing treatment, and improved when the administration of the drug was stopped. Three cases showed jaundice; this symptom was present at time of admission in one of the patients who died (CASE 40324, H. T.), and in the other two it was impossible to say whether it was due to the drug or to the infection.

Cyanosis was not observed in any of the patients who recovered, but was observed in the terminal stages of the dying patients. This lack of cyanosis is in marked contrast to its frequent presence in patients being treated with sulfanilamide and sulfapyridine.

Gross hematuria was not seen in any case, but microscopic hematuria was found in three patients.

Dermatitis occurred in one case and was morbilliform in type.

In no case was hemolytic anemia seen. Granulocytopenia occurred in the patient, H. T. (CASE 40324), to whom we have previously referred and who was admitted with jaundice, a serum bilirubin of 7.1 mg., and empyema. After giving the drug there was a fall of leucocytes from 13,800 to 2,500, and a decrease of granulocytes from 68 per cent to 8 per cent occurred within 2 days. In one other case a fall of leucocytes from 14,500 to 4,500 was seen, but this patient recovered completely.

DISCUSSION

Our experience with sulfathiazole has convinced us that it is an effective drug in the treatment of pneumonia in infants and children. Recovery from the pneumonia was accelerated, and complications were not frequent or troublesome. The drug was administered easily and did not appear to cause the patients discomfort to the same extent as did sulfapyridine. Both drugs have so altered the course of pneumonia that few of the long, hard cases with cyanosis, delirium, abdominal distention, and circulatory failure are seen.

The five deaths which occurred were all in infants in the first year of life. In two of these infants, the administration of sulfathiazole was inadequate because of the moribund state of the patients. Two of the deaths occurred in infants with mongolism, and at necropsy one of these showed a patent interventricular septum. One of the patients showed marked jaundice when treatment was begun. Of those dying, only one

patient was without serious complication at the time when treatment was begun. This child was very toxic, having a temperature of 107° F. at the time of admission.

While it is felt that sulfathiazole is a safe drug in the treatment of pneumonia, it is also felt that the most careful laboratory control must be observed. Particular attention is called to the occurrence of microscopic hematuria and the possible renal changes which this may indicate.

Sulfathiazole and sulfapyridine have materially lessened the length of stay in the hospital and have reduced very appreciably the amount of nursing service required by the patients. There has also been a large reduction in the amount of oxygen used for these patients.

TABLE III

SUMMARY OF CASES

Recovered		162	
Died			
Inadequately treated	2		
Adequately treated	3		
		5	
Total cases		167	
PLEURAL EFFUSION			
Recovered			
Sulfathiazole alone			
Promptly		2	
After 25 days		1	
			3
Sulfathiazole, serum, and thoracotomy			1
Sulfathiazole and serum			1
Sulfathiazole and sulfapyridine			1
			6
Died			1
Total cases			7
OTITIS MEDIA			
Catarrhal		56	
Suppurative		31	
Mastoiditis		0	
Total cases		87	

CONCLUSIONS AND SUMMARY

1. One hundred and sixty-seven cases of pneumonia were treated with sulfathiazole, the dosage being based upon body weight.

2. One hundred and sixty-two of these patients recovered and 5 died. All patients who died were less than 1 year old.

3. Pleural effusions occurred in 7 patients. One of these died and was found to have multiple staphylococcic pulmonary abscesses. Operation was necessary in one case in which sulfathiazole was ineffective, and Type XXXI antipneumococcus serum was given. In one case sulfathiazole was ineffective, and Type VI antipneumococcus serum was used

with success. In one case sulfathiazole was ineffective, and sulfapyridine was used with success. In three cases sulfathiazole was effective in causing the pleural exudate to resolve.

4. Toxic effects were largely gastrointestinal, consisting of vomiting and diarrhea, and were mild in comparison to similar effects caused by sulfapyridine.

5. Sulfathiazole is equally as effective as sulfapyridine in producing critical falls of temperature in patients with pneumonia. It is questionable if there is any difference in promptness of action between the two drugs.

6. Used in moderate dosage over a brief period of time, sulfathiazole has proved to be a safe drug and is easy to administer to young children and infants.

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1740 Bainbridge Street

AN EVALUATION OF ENZYME TREATED MILK IN INFANT FEEDING

MAURICE L. BLATT, M.D., ELLIS H. HARRIS, M.D.,
HOWARD M. JACOBS, M.D., AND MARY ZELDES, M.D.
CHICAGO, ILL.

A COMPARISON of the rates of infant morbidity and mortality due to gastrointestinal disturbances prior to 1900, with those since that time, demonstrates a significant reduction. This reduction has been concomitant with improvement in infant feeding. The problem of artificial feeding occupied so large a part in the lives of the older pediatricians, and had been so improved by them, that Finkelstein made the statement to one of us a few years ago that "the pediatrician is a dying race." However, the present-day incidence of "dyspepsia," although substantially reduced from that of forty years ago, indicates that perfection has not yet been attained; and the ever-increasing knowledge of physiology, digestion, and nutrition continues to stimulate interest in infant foods and infant feeding. McLester[1] recently pointed out "that whereas in the past science has conferred on those peoples who availed themselves of the newer knowledge of infectious diseases better health and a greater average length of life, in the future science promises to those races who will take advantage of the newer knowledge of nutrition, a larger stature, greater vigor, increased longevity, and a higher level of cultural attainment." The pediatrician applies McLester's concept to the modification of milk for artificial feeding, since it is the food of choice and constitutes almost the sole article of diet for the young infant. Continued interest in milk modification has resulted in improvement in growth and development and reduction in infant morbidity and mortality.

It is generally recognized that the character of the curd formed in the stomach is an important factor in the infant's digestion of milk. Brennemann's[2] classic report in 1913 established the fact that the hard large coagula of unmodified cow's milk offer "serious difficulties in digestion." Since the publication of this observation, every method of successfully modifying cow's milk for infant feeding has consciously or unconsciously applied the fundamental principle of reducing curd tension. Dilution, alkalinization, acidulation, heating, addition of cereals, lime water, and colloids such as gelatin, and special processes such as evaporation, drying, homogenization, and base exchange treatment reduce curd tension. These methods have been successful in facilitating digestion, but are attended by the disadvantage of unfavorably altering the chemical composition, the vitamin content, or the caloric value of the milk.

From Children's Division, Cook County Hospital, and St. Vincent's Infant and Maternity Hospital.

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Digestive enzymes have also been used as a method of modifying cow's milk. Chymogen, peptonized milks, and Finkelstein's Eiweiss are examples of such modifications. The enzyme combines with the casein to form a curd which later must be finely divided by mechanical means in preparation for feeding. This process produces a small preformed curd. Once having been formed, and the enzyme inactivated by heat, the curds do not tend to agglomerate when they reach the stomach. The unpleasant flavor, often causing the infant to refuse the formulas, and the time consumed in their preparation are disadvantages associated with their use.

A new method of introducing a proteolytic enzyme into raw milk for the purpose of reducing curd tension, and, at the same time, conserving the essential elements, was developed in 1936.* In this procedure a pancreatic proteolytic enzyme is added to the milk in the dairy plant prior to pasteurization. The enzyme is introduced in the "holding" tank, acts while the milk is being warmed, and is inactivated at the pasteurization temperature of 145° F. This treatment reduces curd tension below 20 Gm., producing a "soft curd" milk. The curd, observed in vitro in Store's artificial stomach, is finely divided, flocculent, and soft. Because of this characteristic, the necessity for further modification of the curd by "kitchen" boiling is eliminated and the associated possibilities of bacterial contamination are reduced as will be shown later. The flavor of the milk is not impaired and the chemical composition is not appreciably altered by this procedure. No detectable hydrolysis of milk protein occurs.

Conquest and co-workers[3] conducted animal feeding tests with this product. They found that calves fed ordinary pasteurized milk retained 23 per cent more curd in their stomachs than did those fed enzylac. The tension of the curds from the untreated pasteurized milk, as measured by the Hill curdometer, was twice as great as that of the curds from enzyme treated milk, in the same experiments. Conquest analyzed the milks chemically, and his titration results for P_2O_5, calcium, magnesium, protein, and the formol values demonstrated that no significant quantitative chemical change results from this type of enzyme treatment. He showed that the enzyme action is stopped by pasteurization before the milk proteins are appreciably reduced.

Our study concerns itself with the growth and development of infants fed enzylac, and with the advantages of feeding this fluid "market" milk without intermediate boiling. It was begun after animal experiments, chemical analyses, and bacteriologic research indicated that the milk complied with accepted standards. Our report is based on clinical observations, anthropometric measurements, and laboratory studies of the children at St. Vincent's Infant and Maternity

*Milk so processed is identified as enzylac. One part of the enzyme is added to 20,000 or 30,000 parts of raw milk, the proportion depending upon the original curd tension and the softness of the curd desired in the finished product.

Hospital, and on weights and stools of premature infants at Cook County Hospital.

Procedure.—The modified milk,* processed by a dairy specialty company, was supplied to the dairy plants delivering to the hospitals in which the study was made. Because of this double method of handling, thirty-three hours elapsed between pasteurization and preparation of the formulas for the succeeding twenty-four hours. Thus, the last feeding offered to the infant each day was a milk pasteurized fifty-seven hours previously. This is in contrast to the usual procedure in which milk is delivered within six hours, permitting the consumption of the last feeding within thirty hours after pasteurization.†

Daily observations of the bacterial counts and curd tension of ordinary pasteurized and pasteurized enzyme milk were made in several laboratories during the course of the study. The average agar plate count of enzylac milk (300 observations) was 11,162 as compared with a count of 13,411 in ordinary pasteurized milk (252 observations). The average curd tension of the enzylac samples was 12; of the ordinary pasteurized milk, 26.

Determinations of blood serum calcium and phosphorus, hemoglobin, and complete blood counts were done on the children at St. Vincent's. The Evelyn photoelectric colorimeter was used for all chemical determinations. For hemoglobin, it was standardized to 15.6 Gm. equalling 100 per cent, in accordance with Van Slyke readings, and based upon Diamond's[4] findings.

Sampling.—Two groups of children were studied. Those in Group I were full-term infants, initially seen during their first four weeks of life and observed for various periods up to their thirty-sixth week. Group II was made up of premature infants, observed from birth. Each group was separated into two divisions of children of like ages. One division was fed enzyme treated and one control milks, supplementary food being identical for each. Human milk, boiled pasteurized, unboiled pasteurized, and evaporated milks were fed to the control divisions. Weight, height, head and thoracic circumference, lateral and anteroposterior diameter of the chest, and intercrestal distance were recorded at intervals of two weeks. All measurements were subjected to statistical analyses, but in order to conserve space, only the graphs of weight and height are shown (Figs. 2 and 3).

The technique and equipment used in taking measurements were described by one of us previously.[5]

RESULTS

Fig. 1 is a typical record of a full-term infant (Group I). The diet, the increase in weight, and the stool frequency are plotted at weekly

*Permission for the preparation of this milk was granted by Dr. Herman N. Bundesen, president of the Chicago Board of Health. The Dairy Specialties Company produced the milk in accordance with Chicago regulations governing pasteurized milk.

†The delay in handling and delivering the milk used in this research has been obviated since the milk is now available commercially.

intervals. Enzylac was used for the initial formula and was continued throughout infancy. The birth weight was more than doubled at 6 months.

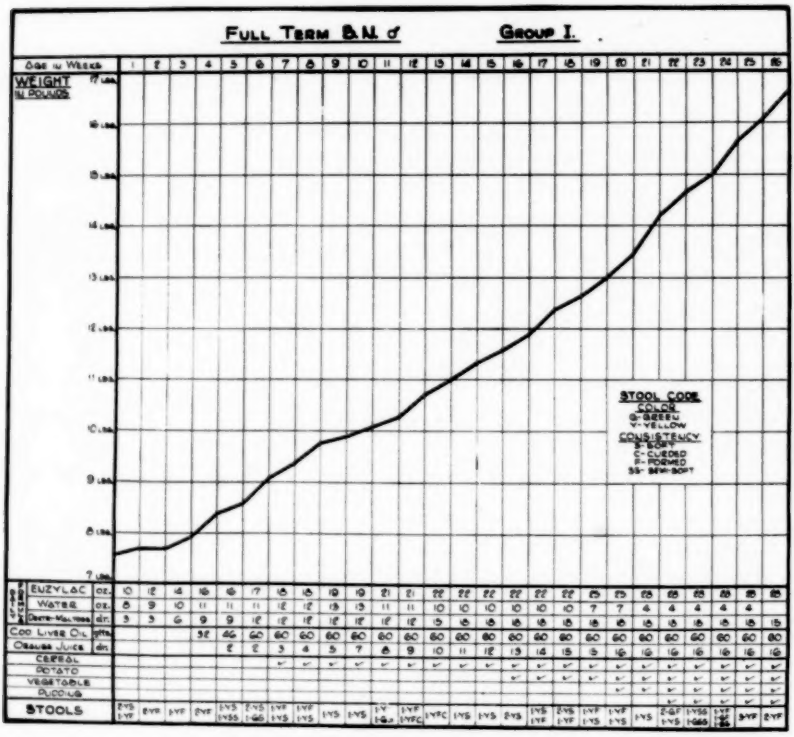

Fig. 1.—Full-term infant B. N. Record of weight, formulas, and stools charted on the seventh day of each week for six months. The initial feeding was enzylac. Birth weight (7 pounds 9 ounces) was more than doubled at six months (16 pounds 10 ounces).

Figs. 2 and 3 demonstrate the mean rate of growth of the children in Group I. All infants came under our observation during the first month of life. Seventy-five were placed on enzylac; of these, eleven remained under observation for twenty-four weeks. Sixty-four were discharged from the institution before the termination of the problem. Thirty-eight were placed on control milks and seven remained at the end of twenty-four weeks; thirty-one were discharged from the hospital during the interim. Since the number of children is not identical in each period of observation, broken line graphs are used. The break in the lines occurs at four-week intervals and represents the average weights of the children remaining at that time.

It will be noted from these graphs that the mean weight and height of the children in the enzylac and control groups are nearly parallel

in every instance, and the trend follows that of the normal growth expectancy. All measurements were greater in the control than in the enzylac group at the onset of the problem, and this relationship existed at the termination.

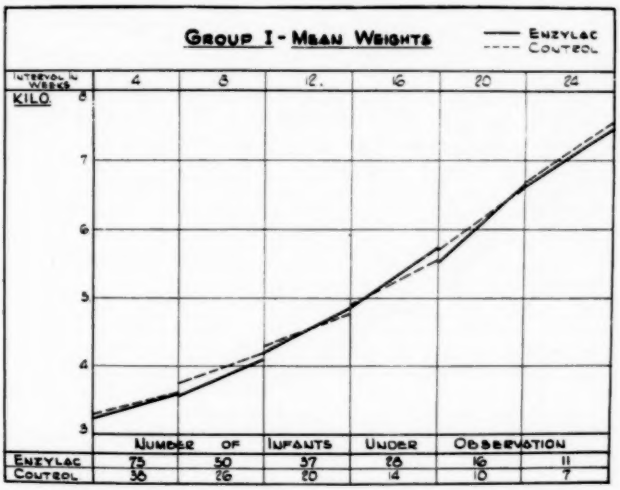

Fig. 2.—Comparison of the mean weights of infants on enzylac and those on control milks.

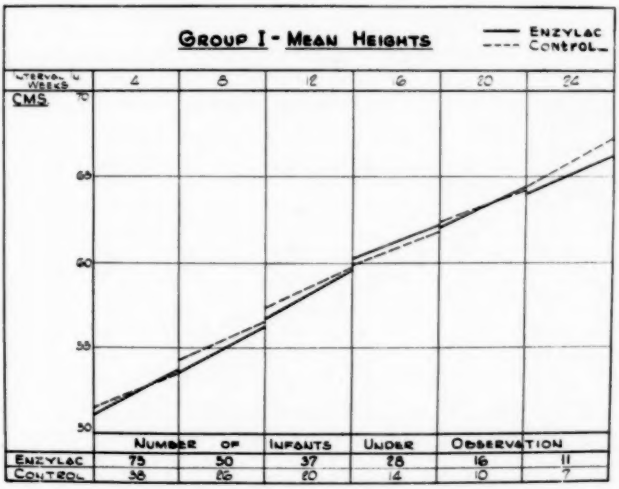

Fig. 3.—Comparison of the mean height of infants fed enzylac and control milks.

Statistical study of these measurements demonstrates that there was no significant difference between the two groups, as shown by standard

error calculations of the difference of the means[6] for each measurement of growth both at the beginning and at the end of the observation period. The level of significance used in statistical analysis was X = 1.96. Values of 1.96 or under give a chance of 95 out of 100 or better that the two groups compared are alike.

Table I is a record of the stool frequency distribution of the full-term infants (Group I). Fifty-five per cent of those fed control milks, in contrast with 44 per cent of those fed enzylac, had more than two stools per day. Assuming that the number of stools is an indicator of the digestibility of an infant's food, it would seem that enzylac was better tolerated than the control milks.

TABLE I

GROUP I. STOOL FREQUENCY DISTRIBUTION

DIET	NUMBER OF INFANTS	FREQUENCY (%) OF NUMBER OF STOOLS PER DAY					
		1	2	3	4	5	6
Enzylac	75	2.4	53.6	33.0	8.1	2.4	0.37
Control milks	38	2.1	43.0	40.5	10.2	3.6	0.36

That enzylac was better tolerated than the control milks is further demonstrated by the fact that 42 per cent of the control division developed a diarrhea at some time during the period of observation. A significantly smaller percentage, 29.3 per cent, of those on enzylac developed diarrhea, as shown in Table II.

TABLE II

GROUP I. INCIDENCE OF DIARRHEA AND OF UPPER RESPIRATORY TRACT INFECTIONS

DIET	NUMBER OF CHILDREN	UPPER RESPIRATORY TRACT					DIARRHEA
		NUMBER AND PERCENTAGE INFECTED	GRADE OF INFECTION*				NUMBER AND PERCENTAGE AFFECTED
			1	2	3	4	
Enzylac	75	(29) 38.6%	75%	25%	0	0	(22) 29.3%
Control milks	38	(20) 52.6%	70%	20%	5%	5%	(16) 42.1%

*Severity of upper respiratory tract infection is graded: (1) Axillary temperatures to 100° F., pharyngitis; (2) axillary temperature to 100° F., rhinopharyngitis, postnasal drip; (3) axillary temperature to 101° F., profuse nasal discharge, nonsuppurative otitis media; (4) axillary temperature over 101° F., rhinopharyngitis, sinusitis, suppurative otitis media, bronchitis.

Diarrhea is defined as an incidence of three or more liquid, or very soft, stools in twenty-four hours. Periods of observation ranged from six to thirty-two weeks on individual infants.

It will be noted from Table II that fewer infections of the upper respiratory tract occurred in the infants fed enzylac than in those in the control division.

Routine blood examinations of the two divisions in Group I were made from birth to 36 weeks of age. There was no significant difference in the cytology or blood chemistry of the enzylac and control groups. Both conform fairly closely to the usually accepted standards for these ages.

The weight gains of seventy-one premature infants (Group II) fed enzylac and of a like number on control milks were studied. In both divisions the infants had been originally fed breast milk. They were paired on artificial feeding during the same number of days and were approximately the same ages. The seventy-one premature infants fed enzylac gained a total of 654.25 oz. during an observation period of 909 days; the average gain per day was 0.72 oz. Seventy-one premature infants fed control milks gained 544.25 oz. during an observation period of 909 days; the average gain per day was 0.6 oz. The group on enzylac averaged a daily gain of 0.12 oz. (20 per cent) more than did the group on the control milks. The average number of stools per day was approximately the same in both divisions. The infants on enzyme treated milk tolerated it well, and their gain in weight was more rapid than that of the control group on other artificial foods. Since the compilation of these statistics, several hundred premature infants have been fed this product. Their rate of gain and the number of their stools per day corresponded closely to those observed while on human milk, the ideal food for the premature. No instance of intolerance has been observed.

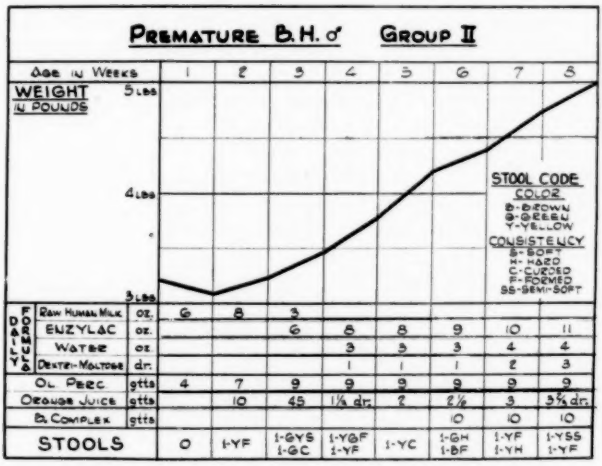

Fig. 4.—B. H., premature negro male. Record of weight, formulas, and stools charted on the seventh day of each succeeding week of life. The infant was discharged during the eighth week when the weight was over 5 pounds.

The formulas, number and character of the stools, and the weight curve of a typical infant in Group II (prematures) is shown in Fig. 4. This graph demonstrates the method and success of initial feeding of raw breast milk and subsequent substitution of unboiled enzyme treated milk. Unboiled enzylac was introduced as partial replacement of breast milk in the third week of life when the infant weighed 3 pounds 5 ounces; during the following week breast milk was completely re-

placed by enzylac. The infant's progress was uneventful and satisfactory. This graph demonstrates our usual routine and results.*

DISCUSSION

Recognition of the significance of the character of the curd formed in the human stomach is an important advance in the study of the digestion of milk. The subject has received much attention both in dairy research and in infant feeding in the last three decades.

Following Brennemann's and Ibrahim's pioneer experiments, Hess[7] studied the digestion of various milk modifications in vitro and when fed to puppies. He concluded that the value of modification is, first, in the formation of soft, easily broken curds, exposing large surface areas to the action of the digestive juices, and, second, in the denaturization of proteins.

The mechanical determination of the curd tension of milk was introduced as a simple and exact method for predicting the type of curd that would be formed after ingestion. This advance followed Allemann and Schmid's[8] research on curd tension in relation to commercial cheese production. They devised an apparatus for determining the force needed to cut curd in vitro. Buckley[9] classified milks from different breeds of cattle on the basis of curd tension. Hill[10] improved the mechanism and technique for its determination. In his study he found a range of from 15 to 200 Gm. in the curd tension of different samples of cow's milk. He reported that tension was reduced approximately 69 per cent by boiling and that pasteurization had a much less pronounced effect. Hill evaluated the clinical reports of a number of observers, and concluded that "feeding tests with infants so far observed, indicated that the physical curd character of the milk, as determined by use of the curd test, is an index to the comparative digestibility of the milk by delicate infants." Doan and Flora[11] more recently carried out studies "to obtain definite information relative to the accuracy of curd tension measurement as an index of the digestibility qualities of various types of soft curd milk," in order to evaluate them for infant use. They concluded, in part, that "curd tension value does not appear to be a reliable index of digestibility for all types of milk. Curd particle size apparently would be a more accurate index of the digestibility of milk and its suitability for use by infants than is curd tension." Store has demonstrated that the curd particles formed in the digestion of enzylac are very small, and our research, we believe, shows that this product conforms to Doan and Flora's premise.

*Our routine feeding schedule for premature infants is as follows: (1) All are initially fed raw human milk; (2) oleum percomorphum is added on the second day of life and orange juice on the fourteenth day; (3) unboiled enzylac is introduced at two weeks of age if the infant then weighs 3 pounds or more; (4) if the birth weight is more than 3½ pounds, unboiled enzylac is put into the formula during the first week; (5) approximately 2 oz. of undiluted raw human milk, undiluted enzylac, or a combination of the two, is fed per pound of body weight per day; (6) later water and dextrimaltose are added; (7) weak tea is fed between formula feedings.

The factors which determine the curd tension of natural cow's milk were studied exhaustively by Weisberg.[12] After correlating the quantitative measurements of viscosity, conductivity, and buffer action, he expressed the opinion that the suspensoid phase differentiates a soft from a hard curd milk.

The complex composition of milk makes it difficult to evaluate the factors that determine curd tension and are responsible for its artificial reduction. To quote Holm,[13] "Milk is a colloidal system composed of several phases varying in their degree of dispersion. The continuous liquid phase may be viewed as a water solution of lactose, various salts, and soluble proteins (albumin, globulins, etc.); and the suspended phases, as fat, calcium caseinate, and some colloidal calcium phosphate, suspended in the homogenous phase in very fine states of division.

Espe and Dye,[14] in a series of experiments, were able to show clinically that doubling the curd tension of milk increases the length of the digestive period from 30 to 65 per cent. Doan and Welsh,[15] studying the problems of soft curd milk by observing the emptying time of the stomach, concluded, after a series of regurgitation experiments, that soft curd milk leaves less residue in the stomach after a given interval than does milk having a high curd tension.

Jeans and Stearns[16] showed that soft curd milks are well tolerated and utilized by infants and children. Morris and Richardson[17] have reported clinical success in feeding soft curd milks.

In our study with unboiled, pasteurized, enzyme treated milk it was realized that feeding milk without boiling was a radical departure from the methods commonly practiced in infant feeding. That such a procedure is without danger is evidenced by the extensive reports which have been published showing the bacteriologic safety of milk after pasteurization. Park[18] published a review of the work on the thermal death point of pathogenic bacteria in milk. He showed that the usual holder pasteurization procedure kills the common pathogen and allows an adequate margin of safety. Other authors have shown that the "majority thermal death point" is obtained by pasteurization and that acid-forming organisms which survive are not only without pathologic significance, but seem to be desirable. The survival of nonpathogenic acid-forming organisms may be a factor in the lower incidence of upper respiratory tract infections in the infants fed enzylac than in those in the control groups. Furthermore, it is believed that the greater frequency of infections of the upper respiratory tract occurring in our groups fed hot processed and evaporated milks, i.e., controls, indicates human contamination of the milk during its formulation and overgrowth of the organisms during the cooling process.

The bacterial content of both the enzylac and the ordinary pasteur-

ized milk was checked by daily plate counts.* Both milks were received, with few exceptions, at a bacteriostatic temperature of below 50° F. The plate counts averaged 11,000 per cubic centimeter for enzylac, and 13,000 for ordinary pasteurized milk. This more than satisfies the public health regulations which require a count of less than 30,000 per cubic centimeter. The samples tested have been subjected to the usual vicissitudes of commercial handling.

To further check the efficiency of pasteurization of the milk used and the inactivation of the added proteolytic enzyme, quantitative tests for phosphatase were run frequently in our laboratories. The significance of this test was established by Edwin Schorer[19] in 1912. He showed that all the indigenous enzymes of milk were inactivated by efficient pasteurization, and demonstrated that their quantitative presence could be used to determine the completeness of pasteurization. The phosphatase test is used by the Chicago Board of Health and many other public health agencies for this purpose. This test is so delicate that, according to Kay and Graham,[20] "1.5° F. under pasteurization temperature, or ten minutes under pasteurization time, or the admixture of 0.25 per cent of raw milk is detected." According to these authors, the presence of less than 1.9 units of phosphatase indicates adequate pasteurization, and readings above 1.9 units, inadequate pasteurization. We employed the chemical method of Kay and Graham, and the more delicate Evelyn photoelectric colorimeter for the final color determinations. All the readings were below 1.6 units in both the pasteurized and pasteurized enzyme milk. The daily bacterial plate counts and the phosphatase tests over a period of three years indicate that pasteurization in the Chicago area is more than satisfactory. The Chicago Board of Health and the dairy plants are to be commended for the cooperation and efficiency evidenced in these results.

We observed that the preparation of formulas from cold pasteurized low curd tension milk saved time, labor, and expense incident to boiling, and reduced the cost of refrigeration. These factors are of importance in both the home and hospital. An element of even greater importance is that of improved bacteriologic control. The preparation of milk formulas using only cold ingredients introduces the factor of bacteriostasis, an element of bacteriologic safety not present when warm or hot constituents are mixed. A temperature of 50° F. or below is essential for the preservation of market milk. There is, consequently, a lower bacterial count at the end of twenty-four hours in formulas prepared and stored at a bacteriostatic temperature than in those prepared with hot milk. With proper refrigeration, a low plate count is maintained until the formula is consumed by the infant, be-

*The facilities of the following laboratories were used: The Bacteriological Department of the University of Illinois, College of Medicine, under the direction of Lloyd Arnold, M.D.; the Research Laboratories of Armour and Co., under the direction of Victor Conquest, Ph.D.; the Bacteriological Laboratories of Cook County Hospital; the Clinical and Research Laboratories of St. Vincent's Infant and Maternity Hospital under Miss C. Korteum, R.N., M.T.; and the Laboratories of the Chicago Board of Health. The bacterial flora and pH of the stools will be made the subject of a later report.

cause organisms accidentally introduced into the cold milk multiply slowly, if at all. On the other hand, indigenous nonpathogenic thermostable and thermophilic organisms, contaminants from the air, and organisms introduced by human contact into hot milk formulas multiply with extreme rapidity during a prolonged cooling period. The refrigerator becomes an incubator when its temperature is above 60° F. We have observed that the temperature of the refrigerator remains well above 50° F. and often as high as 70° F. from six to twelve hours after it has been loaded with hot milk formulas. In the same refrigerator, a constant temperature of 50° F. or lower was maintained when cold milk formulas were stored. Table III[21] demonstrates the effect of storage temperature on the changing bacterial content of milk. The bacterial counts of the twenty-four-hour milk, held at 50° F. (Table III), are approximately the same as the counts of pasteurized milk delivered to the home, as determined in our investigation.

TABLE III

GROWTH OF BACTERIA IN MILK AT VARIOUS TEMPERATURES

TEMPERATURE (°F.)	CONDITION	AVERAGE NUMBER OF BACTERIA PER C.C.			AVERAGE RATIO OF GROWTH		
		FRESH	24 HR.	48 HR.	FRESH	24 HR.	48 HR.
40	1	4,295	4,138	4,566	1	1.25	1.21
50		4,295	13,961	127,727	1	3.24	31.07
60		4,295	1,587,333	33,011,111	1	398.60	8,772.10
40	2	39,082	88,028	121,864	1	2.40	3.80
50		39,082	177,437	831,615	1	6.70	24.30
60		39,082	4,461,111	99,120,000	1	351.00	6,114.80
40	3	136,533	281,646	538,775	1	2.47	4.62
50		136,533	1,170,546	13,662,115	1	14.68	137.94
60		136,082	24,673,571	639,884,615	1	759.90	25,308.00

The ratio of growth represents the multiple by which the count in the fresh sample was increased by the respective holding temperatures and times. For each sample the ratio of growth was computed, and these ratios were averaged. Because of this, the ratios given above do not agree exactly with the ratios that might be computed from the average bacterial counts.

The conservation of the indigenous vitamin and mineral constituents of milk enhances its value as an infant's food. This is of particular importance during the early weeks of life when the nutritional need is supplied entirely by milk. With the exception of iron, the mineral requirements of the young infant seem to be adequately supplied by cow's milk. The need for a liberal calcium and phosphorus intake is well recognized. Sherman's[22] observation in this regard seems particularly significant. He states that "in the evolution of human anatomy and physiology, there was doubtless 'survival value' in the baby born with flexible bones [an obvious advantage to both mother and child so far as the event of parturition is concerned, discussed further in the writer's "Food and Health," 1934]. But this means being born with calcium-poor bodies which must increase their percentage, not merely their amount, of calcium during their growth and development. Hence, there is an accentuated need for calcium (and for phosphorus) over the need for body-building material in general. Thus, the calcium

and phosphorus requirement of growth are relatively higher than the protein requirements of growth. And unless the food furnishes the relatively liberal calcium intake required for optimal calcium retention, the growing body will remain calcium-poor for an unduly long time." In view of these facts, the use of a milk in which minerals have been removed for the purpose of reducing curd tension does not seem advisable for infant feeding.

It has been shown by Kon[23] and co-workers that pasteurized milk has a higher nutritional value than superheated milk. Their conclusions were based on studies on rats. They demonstrated that the sterilization of milk by superheating, i.e., autoclaving, reduced the biologic value of the protein by 6 per cent, vitamin C, 50 per cent, carotene, 2 per cent, and vitamin B_1, 30 per cent. The wide use of evaporated and boiled milk in infant feeding makes recognition of these losses important. Because pasteurization causes less loss than boiling or evaporating, it would seem logical to use pasteurized milk in artificial infant feeding whenever practical, thus conserving the vitamin and caloric content. With our rapidly increasing, but inadequate, knowledge of optimum vitamin requirements, it seems most desirable not to destroy what nature has supplied in cow's milk. Cold processing of low curd tension milk would seem to meet these requirements more nearly than do other methods of milk formulation.

SUMMARY

Market milk was treated with a pancreatic proteolytic enzyme just prior to pasteurization. The addition of the enzyme so reduced the curd tension that boiling, for formulation for infant feeding, was found unnecessary. The curds formed from this milk are soft, flocculent, finely divided, and do not tend to agglomerate. The enzyme treatment does not alter the appearance, taste, or cream line of the milk.

This milk has been fed at St. Vincent's and Cook County Hospitals, to the premature, newborn, and older infants during the past three years. It has been used either diluted or undiluted in accordance with the usual method of prescribing infant formulas. Several thousand infants were fed this unboiled milk. Observations did not reveal a single instance of milk intolerance. Curds were rarely seen in the infants' stools.

The physicochemical change which takes place when the enzyme is added is not definitely known. It is presumed that some change takes place in the calcium casein bond, resulting in denaturization of the casein. The enzyme is inactivated by pasteurization, just as are the indigenous enzymes of milk.

The preparation of an infant's food, using cold unboiled milk, cold water, and cold sugar solutions, eliminates the dangerous bacterial multiplication that occurs during the cooling phase of previously heated solutions. Elimination of boiling large quantities of milk re-

duces the cost of preparation and refrigeration and materially increases the comfort of the workers in the milk kitchen.

Our observation demonstrates that the growth and increase in overall measurements of the infants fed enzylac compare favorably with those in a control group on formulas made with other milks and by other methods. When subjected to statistical analysis, the difference between the two groups is not appreciable.

Less diarrhea and fewer infections of the upper respiratory tract occurred in the groups fed cold processed enzylac than in those fed control milks.

CONCLUSIONS

The addition of a pancreatic proteolytic enzyme to milk prior to pasteurization reduces the curd tension.

The curd formed from milk treated with this enzyme is soft, flocculent, finely divided, and does not tend to agglomerate.

By eliminating boiling, danger of bacterial overgrowth from contaminants and the labor and cost of formulation are reduced.

"Cold processing" increases the comfort of the workers in the formula laboratory.

Newborn, premature, and normal infants tolerate enzylac well, develop normally, and, in this study, have less diarrhea and infection of the upper respiratory tract than those in a like environmental situation on control milks.

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PROTHROMBIN IN THE NEWBORN INFANT

Relationship to the Maternal Dietary Vitamin K Intake

Simon Kove, M.D., and Henry Siegel, M.D.
Brooklyn, N. Y.

INCREASING interest is being centered on vitamin K and its relationship to abnormal conditions in infants. In view of the conflicting reports of normal prothrombin levels in newborn infants, we feel that further studies are indicated. Furthermore, investigation into the cause of the wide variations is essential if we are to obtain a clearer concept of the value of vitamin K in the neonatal period.

The existence of an antihemorrhagic vitamin was first demonstrated by Dam in 1929.[1] Since then, considerable information has accumulated concerning this accessory food factor. The isolation of vitamin K in crystalline form has been reported recently, and it appears to have a quinone structure.[2] It is fat-soluble and is found in large quantities in the green leafy vegetables, being especially rich in alfalfa. Other rich food sources of vitamin K include putrefied fish meal, hog-liver fat, kale, spinach, dried carrot tops, tomatoes, soybean oil, cabbage, and cauliflower.[3] Almquist and his associates[4] have demonstrated that it is also produced as a result of bacterial metabolism in the feces.

The vitamin acts by maintaining the level of prothrombin in the blood. In the absence of vitamin K, the prothrombin concentration falls. The exact mechanism involved has not as yet been determined. It is believed that the liver is involved, for, if it is injured, a drop in prothrombin level follows, despite the administration of vitamin K.[5] Clinically and experimentally, bile has been found essential for its absorption.

Prothrombin determinations are expressed in terms of either percentage of normal or prothrombin clotting time. The prothrombin clotting time, according to the method of Quick,[6] is the time required for plasma to clot upon the addition of excess amounts of calcium and thromboplastin. This clotting time is an indirect function of prothrombin concentration. The normal value for prothrombin clotting time varies from ten to twenty seconds, depending upon the potency of the thromboplastin preparation. Values of forty-five seconds or higher imply that hemorrhage may occur.[7] The concentration of prothrombin in the plasma is then determined from a graph constructed to demonstrate the prothrombin clotting time of serial dilutions of normal adult plasma, as suggested by Quick.[6] The prothrombin concentration at which bleeding occurs has been variously estimated to be between 20 and

From the Department of Pediatrics and Pathology, Kings County Hospital. Dr. G. Brockway and Dr. W. W. Hala, directors.

30 per cent of normal, but recently the critical level has been quoted as being as high as from 40 to 50 per cent.[8] The normal value of prothrombin is regarded as being between 75 and 100 per cent.[9] In the two-stage titration method devised by Warner, Brinkhaus, and Smith, the prothrombin level is determined by first converting prothrombin to thrombin and then titrating the latter, using serial dilutions.

Recently, less accurate, but more rapid, methods for prothrombin determinations have been devised, using whole blood rather than plasma. In the bedside test proposed by Smith and his associates,[10] the time required for the formation of a clot upon the addition of whole venous blood to thromboplastin is determined, the normal figure being from twenty to thirty seconds. Kato[11] has devised a microprothrombin method following the general principles of Quick's method but using capillary blood in place of plasma. It must be borne in mind that any method which employs the use of whole blood does not accurately measure the prothrombin level. This results from the fact that the red cells displace significant quantities of prothrombin containing plasma, thus introducing an extraneous factor which is difficult to control in view of varying degrees of red cell volume in different persons.

PROTHROMBIN IN THE NEWBORN INFANT

All investigators agree upon the presence of a prothrombin deficiency in the neonatal period. However, a wide difference of opinion exists concerning the levels of prothrombin at different times in this period. Brinkhaus, Smith, and Warner,[12] using their two-stage titration method, found the prothrombin level of blood taken from the umbilical veins of eight newborn infants to vary between 14 and 39 per cent of the normal adult value. They suggested the relationship between prothrombin deficiency and hemorrhagic disease of the newborn infant and cited one case in which prothrombin was almost absent. In a later article,[13] using Quick's method, Smith and his co-workers reported that determinations on 38 infants from birth to 10 days of age revealed normal prothrombin levels during the first day of life, a fall between the second and sixth days, and a subsequent rise to normal levels thereafter. Waddell and Guerry,[14] working on ten normal newborn infants, found that high prothrombin clotting times were common and that the values varied from day to day in each infant. They found the period of most marked elevation to be between 48 and 72 hours of life and thereafter it tended to fall to a common level. In another series of fourteen cases, working in April, May, and June (their previous investigations had been carried out in February and March), they noted that prothrombin deficiency was less constantly demonstrated than in their previous series.[15] They suggested that a seasonal variation in prothrombin levels may account for the difference encountered. Quick and Grossman[16] performed prothrombin determina-

TABLE I

PROTHROMBIN CONCENTRATIONS OF SEVENTY-SIX NEWBORN INFANTS IN THE FIRST EIGHT DAYS OF LIFE AND THEIR CORRESPONDING MATERNAL DIETARY VITAMIN K INTAKE DURING PREGNANCY

CASE	AGE OF INFANT (DAYS)	RACE	PROTHROMBIN CLOTTING TIME		PROTHROMBIN CONCENTRATION (%)	DEGREE OF MATERNAL VITAMIN K DEFICIENCY
			UNDILUTED PLASMA (SEC.)	DILUTED 1:1 PLASMA (SEC.)		
1	1	W	21	32	50	+++
2	1	W	18	26	66	0
3	1	W	14	20	100	+
4	1	B	22	36	44	0
5	1	W	17	28	62	0
6	1	B	92	900+	<5	+
7	1	W	18	27	64	+++
8	1	W	19	29	58	0
9	1	W	20	29	58	0
10	1	W	20	32	50	0
11	2	B	17	27	64	0
12	2	W	22	35	44	++
13	2	B	17	26	66	++
14	2	W	22	34	46	0
15	2	B	16	23	78	0
16	2	W	16	23	78	0
17	2	W	16	23	78	0
18	2	B	17	24	74	0
19	2	W	33	58	22	0
20	2	B	34	55	25	+
21	3	W	21	31	52	+
22	3	W	20	30	54	0
23	3	W	23	35	44	0
24	3	W	16	22	86	0
25	3	W	17	27	64	0
26	3	W	21	32	50	0
27	3	B	15	20	100	0
28	3	W	19	29	58	0
29	3	B	25	40	38	+
30	3	B	20	32	50	+
31	4	B	19	29	58	+
32	4	B	20	30	54	+++
33	4	W	18	26	66	++
34	4	W	16	26	66	0
35	4	W	18	31	52	0
36	4	W	16	23	78	++
37	4	W	17	23	78	0
38	4	W	17	26	66	0
39	4	W	17	23	78	+
40	4	W	17	23	78	0
41	5	W	17	24	74	0
42	5	W	25	35	44	0
43	5	W	16	23	78	+
44	5	W	17	24	74	++
45	5	B	24	38	40	0
46	5	B	15	23	78	
47	5	B	16	22	86	0
48	5	W	17	25	70	0
49	5	B	17	23	78	+
50	5	B	16	22	86	+
51	5	W	19	27	64	+
52	6	W	17	28	62	0
53	6	W	24	34	46	0
54	6	W	16	26	66	+
55	6	W	16	23	78	0

TABLE I—CONT'D

CASE	AGE OF INFANT (DAYS)	RACE	PROTHROMBIN CLOTTING TIME		PROTHROMBIN CONCENTRATION (%)	DEGREE OF MATERNAL VITAMIN K DEFICIENCY
			UNDILUTED PLASMA (SEC.)	DILUTED 1:1 PLASMA (SEC.)		
56	6	W	16	23	78	
57	6	W	18	28	62	+++
58	6	B	16	22	86	+
59	6	W	25	40	38	++
60	6	B	16	23	78	0
61	6	B	19	32	50	+
62	6	W	21	32	50	0
63	7	B	21	31	52	
64	7	W	16	25	70	
65	7	W	16	21	90	+
66	7	W	18	28	62	+
67	7	B	22	32	50	
68	7	W	15	19	100	
69	7	W	17	24	74	0
70	7	W	16	22	86	0
71	7	W	23	32	50	++
72	8	W	14	21	90	
73	8	W	20	30	54	
74	8	B	19	29	58	0
75	8	W	29	45	34	0
76	8	W	17	23	78	0

tions on thirty-one newborn infants between 1 and 8 days of age. They found that cord blood contains a fairly high concentration of prothrombin, varying between 60 and 70 per cent of the normal adult value. After birth, however, the prothrombin concentration decreases and may reach exceedingly low levels, but it gradually rises again, being normal after the fourth day. Nygaard,[17] in a series of thirty-one normal newborn infants, concluded that the prothrombin time is normal for the first ten hours after birth and then rises, to return to normal after the sixth day. Hellman and Shettles,[18] using the blood from the umbilical veins of eighteen premature infants at birth, concluded that the prothrombin levels of premature infants are extremely low as compared to normal term infants. Kato and Poncher,[11] using a microprothrombin method on one hundred mature infants, found that the prothrombin clotting time was elevated at birth and then progressively decreased, to approach, but not reach, normal values by the ninth day.

Hemorrhagic disease of the newborn infant has been found to be associated with prothrombin deficiency. Several investigators have reported the efficacy of vitamin K in controlling this hemorrhagic diathesis.[15, 17]

The purpose of our investigation has been twofold. Firstly, in view of the conflicting reports, we have attempted to arrive at a more accurate conclusion concerning prothrombin levels in normal newborn infants, using a fairly large series of cases under carefully controlled conditions. Secondly, we have studied the maternal diets during the period of gestation in an attempt to correlate the maternal dietary intake of vitamin K with the prothrombin concentration in the neonatal period.

For our study we have used normal healthy newborn infants from the nursery of Kings County Hospital. This is a large city hospital whose patients are drawn from the lower income group. The prothrombin clotting times of seventy-six different infants were determined according to the method of Quick. The infants were chosen at random and distributed so that there were about ten infants for each of the first eight days of life. In each case, blood was drawn from the external or internal jugular vein just prior to feeding and determinations were made upon both undiluted plasma and plasma diluted 1:1 with physiologic saline. With each group of determinations normal adult controls were used. The thromboplastin preparation used was one yielding a prothrombin clotting time of fifteen seconds for the normal adult undiluted plasma and twenty seconds for plasma diluted to 50 per cent. The concentration of prothrombin was determined in each case from a graph constructed to show the relationship of the prothrombin clotting time to the percentage of prothrombin, using serial dilutions of normal adult plasma. At this point we wish to stress the importance of determinations upon diluted plasma in order to increase the sensitivity of the test. It is likewise of importance that the concentration of prothrombin be evaluated in addition to the prothrombin clotting time. A result in terms of the latter only may not appear particularly abnormal and yet may correspond to a low level of prothrombin. A close examination of the results as shown in Table I and Quick's prothrombin dilution curve[6] will clarify this statement.

In Table I are recorded the results of our investigation. Several interesting facts appear from an examination of these figures. The most impressive single feature is the frequency with which prothrombin deficiency is present. If the value of 75 per cent is accepted as the lower level of normal, then it is apparent that fifty-two (68 per cent) of the total seventy-six cases demonstrate a definite prothrombin deficiency.

TABLE II

NUMBER OF CASES AT VARIOUS PROTHROMBIN LEVELS IN SEVENTY-SIX INFANTS IN THE NEONATAL PERIOD

PROTHROMBIN CONCENTRATION (%)	NUMBER OF CASES
75-100	24
50- 74	39
25- 49	11
0- 24	2

An analysis of these fifty-two cases, as shown in Table II, reveals that in two cases there was a marked deficiency of prothrombin, being practically absent in one, and in eleven cases there was a moderate deficiency. Yet, in none of these infants was there any evidence of hemorrhagic diathesis. This indicates that prothrombin deficiency is not sufficient in itself to precipitate the picture which we associate with hemorrhagic disease of the newborn infant. Some additional factor, or factors, must necessarily accompany a prothrombin deficiency.

That the prothrombin deficiency has no particular racial predisposition is evident from the fact that it occurs with about equal frequency in the negro and white infants.

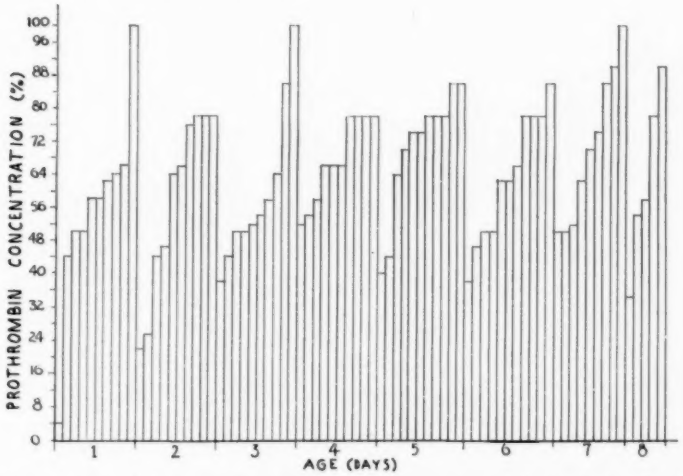

Chart 1.—Prothrombin concentrations of seventy-six newborn infants during the first eight days of life.

Chart 1 graphically demonstrates the prothrombin concentration as related to age in days. It is apparent that wide variations exist in different newborn infants of the same age during the first eight days of life. However, the widest variations appear within the first two days, more commonly on the first day. Again, the prothrombin concentration appears to be at its lowest general level during the first two days and thereafter rises to a somewhat higher value. The general average level, however, remains below the normal adult value on each of the eight days, despite the incidence of normal values in about one-third of the infants.

Our findings may explain satisfactorily the distribution of the initial appearance of symptoms of hemorrhagic disease of the newborn infant in Javert's series of seventy-two cases.[19] He found that hemorrhagic diathesis manifested itself on the first day of life in twenty-five infants, and that thereafter the number diminished progressively with each succeeding day of the neonatal period.

That a prothrombin deficiency exists in the neonatal period appears to be fairly conclusive. The cause of this hypoprothrombinemia however is not as yet clear and is still within the realm of speculation. Prothrombin deficiency may generally be caused by one or several of the following conditions:

1. Diet inadequate in vitamin K
2. Inadequate absorption of vitamin K in the intestines

3. Deficiency or absence of bile in the intestines
4. Liver damage

Quick and Grossman[16] ascribed the low prothrombin level which they found in their cases on the second and third days to an inadequate storage of prothrombin in the fetus. The subsequent rise they attributed to the introduction of bacteria with the ingestion of food and the consequent manufacture of vitamin K in the gastrointestinal tract of the infant by the bacterial flora. Several other factors which may be involved during the first week of life have been suggested by Grossman,[3] namely, inadequate secretion of bile, intestinal hypermotility, and decreased absorptive ability of fat-soluble substances by the intestinal mucosa. Other nonlocal gastrointestinal conditions which he feels may be contributory are deficiency in plasma globulins and the transitory hydremia of the blood which is present during the first few days of life.

MATERNAL DIETARY VITAMIN K INTAKE AND INFANT PROTHROMBIN CONCENTRATION

In the second part of our work we have undertaken to determine whether the maternal diet exerts any influence upon the prothrombin

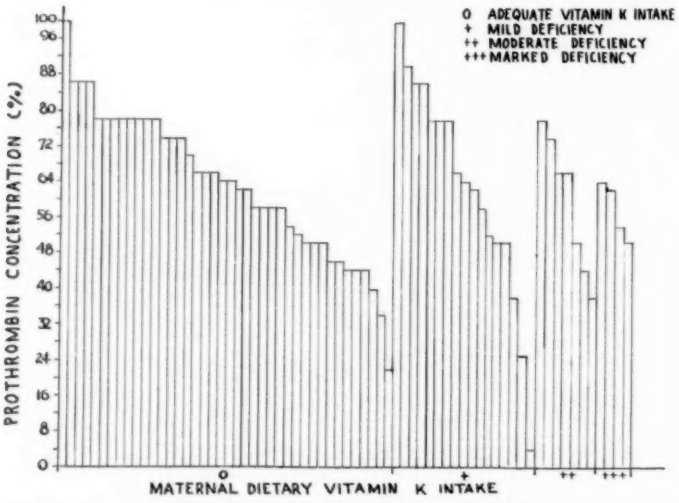

Chart 2.—Showing lack of relationship between infant prothrombin concentration and maternal dietary vitamin K intake.

of the newborn infant. By virtue of the fact that the infants of our series were from low income families, we felt at the outset that the prothrombin deficiency in the neonatal period might well be dependent upon an inadequate maternal diet and, therefore, a deficiency of vitamin K-containing foods. However, when detailed dietary histories were

obtained, we were soon impressed with the relative infrequency of generally inadequate diets, even in this economic group.

In sixty-eight of the seventy-six cases, we obtained a detailed dietary history of the respective mothers during their periods of pregnancy. We then arbitrarily classified the mothers into four groups, depending upon their intake of vitamin K-rich foods as listed previously. In the first group (0) were placed those with diets containing an apparently ample quantity of foods rich in vitamin K. In the second group (+) were those with a mild deficiency; in the third (++), those with a moderate deficiency; and in the fourth (+++), those with a marked deficiency of vitamin K-rich foods in their diets.

From Table I and Chart 2 it is evident that no relationship exists between the dietary vitamin K intake of the mother and the prothrombin level of the newborn infant. In the four cases of marked deficiency in the maternal intake of vitamin K, none of the offspring had a prothrombin concentration below 50 per cent, all being between 50 and 64 per cent. In the single case of almost absent prothrombin, the mother's diet was only mildly deficient in vitamin K. Twenty-eight (70 per cent) of the infants, from the forty mothers with an apparently adequate vitamin K intake, showed a prothrombin deficiency, and ten (25 per cent) of these had a prothrombin level of 50 per cent or less. Of the twenty cases with normal prothrombin levels, only twelve (60 per cent) had an adequate maternal vitamin K intake, seven (35 per cent) a mild deficiency, and one (5 per cent) a moderate deficiency. Of the nineteen infants who showed a prothrombin level of 50 per cent or less, eleven were born to mothers with apparently adequate vitamin K diets, four to those with mildly deficient diets, three to those with moderately deficient diets, and one to a mother with a markedly deficient diet. The same lack of relationship between the maternal intake of vitamin K and the prothrombin level exists on each of the first eight days of life.

COMMENT

These findings demonstrate that the maternal intake of vitamin K-containing foods does not influence the prothrombin level in the offspring. However, we cannot conclude that the vitamin K intake of the mother does not affect the prothrombin concentration in the newborn infant. On the contrary, it definitely does. Experimentally, Almquist, Mecchi, and Klose[20] found low vitamin K reserves in the offspring of chickens maintained on a low vitamin K intake during pregnancy. In human beings, Shettles, Delfs, and Hellman[21] and Waddell and Guerry[15] have conclusively demonstrated that vitamin K administrated in large doses in concentrated form to the mother during pregnancy or during labor will result in elevated prothrombin levels in the newborn infant. The same results may be achieved by giving it directly to the infant at birth.

Why diets which are apparently rich in vitamin K foods should fail to produce a normal prothrombin concentration in the newborn infant with the same consistency as vitamin K in concentrated form, we are not in a position to answer. We can only hazard a few guesses. The most likely explanation appears to be that a quantitative deficiency in the antihemorrhagic vitamin exists even in what apparently is a diet adequate in vitamin K. Or perhaps vitamin K derived from food sources may not be utilized during pregnancy as well as it is in concentrated form. Again, the possibility arises that the requirement of the vitamin is increased in the pregnant state. Be that as it may, the fact remains that we cannot depend solely upon the food sources of vitamin K to assure adequate prothrombin levels in the newborn infant. To produce this desirable effect, vitamin K must be administered in concentrated form to the mother during pregnancy. Since hemorrhagic disease has been proved to be due to, and intracranial hemorrhage has been suggested as being associated with, a prothrombin deficiency, then we have here an important prophylactic weapon in our armamentarium of prenatal care.

CONCLUSIONS

Low prothrombin levels were found in fifty-two of seventy-six infants in the first eight days of life.

Wide individual variations in prothrombin levels occur in each of the first eight days, but most commonly in the first two days.

The average prothrombin level is at its lowest in the first two days and then rises slowly, but remains below the normal adult value.

A study of the dietary history in sixty-eight of the seventy-six cases failed to reveal any correlation between the maternal dietary vitamin K intake and the prothrombin concentration of the offspring.

Therefore, food sources, unlike vitamin K concentrates, cannot be depended upon to assure adequate prothrombin levels in the newborn infant.

Vitamin K concentrates should be given prophylactically to the mother before labor in order to assure elevated prothrombin levels in the newborn infant.

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RECURRENT VOMITING IN CHILDREN

The Factor of Food Hypersensitiveness

Joseph H. Fries, M.D., and Kenneth G. Jennings, M.D.
Brooklyn, N. Y.

THERE is much variation of opinion concerning the specific causes of recurrent vomiting. The authors agree with those who believe that recurrent vomiting* is a symptom complex rather than a disease entity. Such vomiting in children may be due to a variety of causes, among which are metabolic disturbances, acute infections, and organic disease of the gastrointestinal tract and the central nervous system. In addition, hypersensitiveness to foods may be the basis. This paper concerns itself specifically with vomiting resulting from this type of sensitiveness.

The symptoms of recurrent vomiting, regardless of the causes, consist of episodes of persistent vomiting which may become sufficiently severe that even small amounts of nourishment cannot be tolerated. Abdominal pain, headache, or constipation may be associated with the vomiting. The excessive vomiting may result in extreme dehydration characterized by dry skin and tongue, elevated temperature, diminished output of urine, and ketonuria. The attacks last from one to several days and may occur at regular or irregular intervals.

Observations made by the writers on children affected by various allergic disorders have pointed to an allergic basis as one of the possible causes of recurrent vomiting. For example, occasional instances were noted where demonstrable clinical sensitivity to a specific food correlated with positive skin tests and passive transfer tests. The purposeful ingestion of the offending food initiated an attack of vomiting resembling an episode of recurrent vomiting. The avoidance of this food resulted in comparative freedom from attacks. Such specific intolerance to foods suggests an allergic etiology for this type of vomiting, especially when considering that many of these children had other allergic manifestations (such as asthma or hay fever) and/or a positive family history for allergy.

Such clear-cut examples were not our usual findings. In fact, with many of the patients observed, it was difficult to obtain consistent proof, although food hypersensitiveness seemed to be the cause of the recurrent vomiting. Thus, a food which apparently brought on an attack when ingested on one occasion, might fail to precipitate an attack on another

From the Department of Pediatrics and the Department of Allergy, Kings County Hospital.

*Recurrent vomiting as used in this communication is synonymous with the terms cyclic vomiting, periodic vomiting, or acetonemic vomiting of children.

day.* Again, foods which on ingestion gave rise to symptoms of vomiting did not always give positive cutaneous reactions.

HISTORICAL DATA

A number of authors[1-6, 11-18] state in their publications that food sensitivity is one of the basic mechanisms involved in the production of recurrent vomiting, some reporting that the elimination of specific foods from the diet has resulted in the subsidence of symptoms. In these studies, egg was most frequently found to be the offending food; occasionally milk or other ingestants were mentioned. Positive cutaneous reactions to causative foods were obtained with a few of their subjects.[3, 17] Negative skin tests, however, are reported by many of these authors.[3, 10, 13]

Communications primarily devoted to the allergic aspect of recurrent vomiting are few. The report of Hinnant, Evans, and Halpin[16, 23] deals with observations on twenty children with cyclic vomiting. These children comprised 10 per cent of a group of allergic children treated in their clinic. Tallerman[13] discovered a family history of allergy in 45 per cent of forty children subject to cyclic vomiting and in only 25 per cent of control children. The papers of Schloss[3] and Smith[11] contain discussions of the allergic factors of recurrent vomiting in childhood. In the publications of Weichsel,[8] Rowe,[17] Tuft,[21] Clausen[22] and Vaughan,[31] brief mentions are found of the possible allergic etiology of this disorder. In Ott's[15] report, the patients described were of allergic inheritance. In the five cases reported by Glaser and Lerner,[19] two were of allergic lineage.

There is some evidence that this type of vomiting is an equivalent of migraine,[10, 18] which is presumably of allergic etiology.

With regard to the theory that excess fats may be the cause of cyclic vomiting, Bray[10] found that patients with this disorder had normal tolerance for fats, provided the allergenic foods were eliminated.

However, some investigators[9, 18] maintain that no conclusive evidence of an underlying allergic mechanism exists; or, at most, that food sensitivity is only an unimportant precipitating factor.

ALLERGIC FACTORS IN THE PRODUCTION OF RECURRENT VOMITING

Periodicity of Allergic Manifestations.—Allergic manifestations tend to recur in definite attacks which are separated by intervals of complete or partial freedom. (This applies particularly to attacks of bronchial asthma, urticaria, and angioneurotic edema.) Recurrent vomiting tends to follow a similar pattern, and, inasmuch as vomiting may be due to hypersensitiveness to foods, it is not improbable that attacks of recurrent vomiting may also be of allergic origin.

*The writers' question would imply the existence of "refractory periods," or of a daily variation in the "threshold of tolerance."

Combination and Alternation of Symptoms.—The authors have seen allergic children who suffered simultaneous attacks of asthma and of intractable vomiting. In other patients, asthma and vomiting were distinctly separate and sometimes alternating. Severe prolonged vomiting immediately before the onset of an attack of asthma, or directly after an attack of asthma, was also observed. Some patients display all of these combinations. The authors deduce from this that definite patterns of allergic vomiting and asthma exist, built either of a concomitancy or of an alternation of symptoms, or of a combination of both.

Delayed Onset of Vomiting.—When vomiting does not occur immediately after a suspect food is eaten, the tendency might be to regard the ingested substance as innocuous. Allergic manifestations, however, do not necessarily follow directly after the introduction of an allergen. The delayed effect sometimes observed from parenteral injection of pollen and other antigens may be cited.

The Effect of an Increased Tolerance Level.—Delayed onset of vomiting might also be indicative of increased tolerance. The writers observed patients, who, in early childhood, exhibited acute symptoms of vomiting immediately after the ingestion of a specific food, but who, a few years later, ate this food apparently without untoward effect. However, after this tolerance seemed to have been established, mild and dissociated vomiting episodes insidiously reappeared. With certain children, these vomiting episodes disappeared again with the elimination of this food. The following conclusions might be drawn: That vomiting now resulted only from increased or cumulative amounts; and that the reaction time to a specific excitant had become longer.

Cumulation and Synergism†.*—The possibility of cumulative effects from several administrations of the same or of different allergens, as suggested by Cooke,[28] should be considered. Although Cooke limited his discussion to examples of parenteral absorption, it is our opinion that such phenomena may result also from oral absorption.

In Case 3 a cumulative mechanism might have been operative, since a gastrointestinal disturbance resulted only after repeated ingestions of milk.

Recurrent Vomiting and Gastrointestinal Allergy.—Recurrent vomiting and the gastrointestinal syndromes due to food hypersensitiveness

*Sylvester[7] suggested that the recurrent explosive character of allergic manifestations might be due to the cumulative effect of specific allergic stimuli. A "threshold of tolerance" was reached where a small additional amount of the allergen was sufficient to precipitate symptoms. He added, further, that nonspecific factors such as infection, fatigue, or nervous strain might play precipitating roles.

We feel this entire concept of a "threshold"—the nature of the substance which can produce an accumulative effect, and the mechanism by which the symptoms are finally precipitated—is still very vague, even in the minds of those who propose it.

†Some recent communications on the synergic action of antigens as observed in animal experiments may be relevant. Thus, Burky[24, 25] reported that there was a definite increase in the antigenicity of certain proteins (e.g., pollen extracts) when others (e.g., staphylococcus toxin) were admixed. Swift and Schultz[26] confirmed these observations and reported further that, even when the two substances were introduced separately, or at different times, there was an augmented response. Additional confirmation of such synergic antigenicity has been provided by Magerl.[27] However, on the basis of some of his experiments on guinea pigs, Pratt[30] doubts the summation of antigenic effect.

are usually most apparent in early childhood, and, as age advances, both become less severe and generally disappear at puberty. This generalization has been fully justified in the writers' experience. The existence of such a parallelism is of interest because it suggests the possibility of common etiological factors for recurrent vomiting and gastrointestinal allergy.

Roentgenologic Findings.—In their roentgenologic studies of children subject to cyclic or recurrent vomiting, Kerley and LeWald[30] found pylorospasm and abnormal gastric retention. It is our opinion that the pylorospasm evidenced in these roentgenographic studies might have been motivated by food sensitivity, since some of these children were reported as subject to food intolerances. In a communication by Fries and Zizmor,[29] similar spasm of the pylorus, gastric retention, and vomiting were reported in children subject to alimentary disturbances due to food allergy. The reports of Cases 1 and 2 illustrate spasm of the pyloric region of the stomach as associated with ingestion of allergenic foods.

REPORT OF CASES

Six illustrative cases are herewith described. In several of them severe vomiting resembling an episode of recurrent vomiting resulted from the purposeful administration of an allergenic food.

CASE 1.—P. K., a 5-year-old boy, was admitted to the clinic because of asthmatic attacks which had been irregularly recurrent since the age of 3.

There was a positive history for allergy in the immediate family.

Since the age of 2, he had been subject to vomiting attacks of several days' duration. These occurred about twice a year. The mother had been unaware of any specific foods as the cause.

At 6 months of age one-half teaspoon of soft-boiled egg had been given for the first time. Ingestion was followed by immediate vomiting. The patient continued to vomit for twenty-four hours and was unable to retain even small quantities of foods or liquids. Egg had been given again when the patient was 1 year old, whereupon he vomited and remained intolerant to foods for the rest of the day.

Recently the mother attempted to feed egg, but nausea and vomiting have invariably followed. On one of the mornings of his attendance at the clinic, a teaspoon of soft-boiled egg was purposefully given to the fasting patient. After five minutes had elapsed, he began to vomit. Concomitantly, he complained of cramplike pain in the midabdomen; the eyes became congested, the nose clogged, and sneezing ensued. These symptoms persisted in severe form for about three hours. For the following two days, the patient was intolerant to food. He vomited after eating and complained of nausea and abdominal discomfort.

Intracutaneous tests with egg protein (0.0001 mg. N per cubic centimeter) elicited marked positive reactions.

A roentgenologic study of the gastrointestinal tract revealed normal findings. However, a similar study made two weeks later in which one teaspoon of egg had been added to the barium meal (without the knowledge of the patient) revealed the following: Immediately after ingestion, the patient complained of nausea and vomited a portion of the barium meal. On fluoroscopic and roentgenographic examination, evidences of pylorospasm were found; the pyloric end of the stomach failed to fill, and no food was observed to pass through the pylorus for almost one hour. Considerable retention in the stomach was noted after six hours.

Although the patient could not retain egg, he apparently tolerated foods in which eggs were contained and processed (such as cakes, puddings, noodles). These, incidentally, had been part of his diet since early childhood. Since the initiation two years ago of an egg-free diet, from which egg-containing foods were also eliminated, the patient has not had any severe attacks of vomiting.

CASE 2.—P. G., a 6-year-old white male, first came under our observation when 1 year old. The patient's mother had asthma; the paternal aunt had hay fever. It had been noticed that the ingestion of a formula containing cow's milk, which had been fed irregularly since the child was 1 week of age, was usually followed by an episode of vomiting.

This patient had been hospitalized because of a severe eczema involving the entire face and body. Intradermal skin tests to egg (0.001 mg. N per cubic centimeter) elicited a marked positive reaction despite the fact that the patient had not yet received egg as part of his diet. The cutaneous reactions to milk protein were negative.

The patient has been observed in the allergy clinic since then. At 18 months of age, he ate a minute amount of egg yolk for the first time, whereupon sneezing, coughing, and dyspnea ensued.

At 3 years of age, recurrent attacks of nausea and cramplike abdominal pain occurred. These gastrointestinal paroxysms became increasingly severe until episodes of intractable vomiting associated with abdominal pain, constipation, headache, and low-grade temperature were evidenced. These seizures would last about two days. In some instances, foods containing egg seemed to be the cause.

At 4 years of age, the patient developed asthma. Since then, asthmatic seizures have alternated with periods of severe vomiting or attacks of abdominal pain.

When the child was 5 years old, we purposefully fed him a whole soft-boiled egg divided into three portions, administered at hourly intervals. Slight nausea was the only immediate effect noted. However, within twenty-four hours the patient began to vomit and to complain of persistent nausea. Vomiting continued for two days, the patient tolerating only small quantities of liquids. Abdominal pain, headache, constipation, and irregular elevations of temperature were observed concomitantly.

During an interval when the patient was entirely free from symptoms, roentgenologic examination was made with an ordinary barium mixture. Fluoroscopic and roentgenographic study revealed a normal stomach. The pylorus was not spastic, and the duodenal bulb filled well. The barium left the stomach readily. Several days later, a second examination was made by means of an opaque meal in which a small amount of egg was contained. Combined fluoroscopic and roentgenographic study at this time revealed the following: The motility of the stomach was definitely diminished; the barium failed to fill out the pylorus; practically no barium left the stomach for a period of thirty minutes; and the duodenal bulb narrowed and was filled with difficulty.

During the past year the patient has been on a diet from which egg has been carefully excluded, and during this period he has been free of gastrointestinal symptoms. Direct intracutaneous and passive transfer skin tests to egg remain markedly positive.

CASE 3.—T. C., a male child, has had infantile eczema since the age of 6 weeks. On his admission to the clinic at the age of 1 year, the rash had become localized on the cheeks and on the bends of the elbows and knees.

When 5 months old, he was fed a small amount of egg yolk, which he vomited immediately. Three weeks later, he was fed about two teaspoonfuls of soft-boiled egg. No immediate effect was noted. About four hours later, however, he began to vomit and vomited continuously for three days. During this time, the vomiting episodes were frequent, and the child was intolerant to most foods.

In an attempt to "develop a tolerance" for this food, the child was fed egg on four occasions between the ages of 6 months and 1 year. In each instance, prolonged vomiting followed immediately after ingestion of soft-boiled egg; however, it started about five hours after ingestion of hard-boiled egg.

The most recent attempt had been made one week prior to admission to the clinic. An entire egg yolk had been given. Vomiting commenced about seven hours later and continued for five days. During this time the child was intolerant to all foods.

An intracutaneous test with egg protein containing 0.1 mg. N per cubic centimeter resulted in a three-plus reaction.

CASE 4.—H. K., 3 years old at the time of admission to the hospital, had been subjected to attacks of asthma and urticaria since the age of 8 months.

His mother had a marked dislike for milk, the ingestion of which was followed by diarrhea. A paternal uncle suffered from swelling of the hands after eating fish.

Throughout his infancy, the child vomited repeatedly after feedings which contained cow's milk. Episodes of loose mucous stools would occur every three to four months and would last from three to seven days.

At 8 months of age, the ingestion of egg was immediately followed by the appearance of an urticarial rash. At 2 years of age, when a second trial was made, no unusual symptoms resulted.

At 1 year of age, the ingestion of a minute amount of fish caused a severe attack of urticaria. Thereafter, on repeated occasions, the ingestion, inhalation, or contact with fish resulted in an urticarial rash or edematous swellings of the eyelids and face.

The attacks of vomiting and diarrhea to which this patient had been subject since infancy became increasingly severe, until, at the age of 3 years, these periodic upsets were characterized by severe vomiting, abdominal pain, constipation or diarrhea, and low-grade temperature. These episodes would recur every two to three weeks and would last from two to seven days.

At the age of 4, the onset of hay fever symptoms was noted. Skin tests (intradermal and passive transfer methods) elicited at this time marked positive reactions to milk, chicken, fish, lamb, beef, green pea, pork, and ragweed and timothy pollens. There were slight reactions to egg and several other foods.

On several occasions, the trial ingestion of milk over a period of about three to four days resulted in a prolonged episode of vomiting. Similarly, the ingestion of chicken or lamb during the season of ragweed pollination seemed to precipitate such attacks.

At present the child is 6 years old. For the past two years he has been maintained on a diet eliminating the foods to which he reacts positively. Only two attacks of vomiting have occurred during this time.

CASE 5.—D. U., a 6-year-old male, had been subject to recurrent attacks of vomiting since the age of 2. These seizures recurred at approximately three-month intervals and consisted of severe vomiting, abdominal pain, and elevated temperature. They would last from three days to two weeks.

During the past year, they have occurred at intervals of about one month; and for the past two months these episodes have been fairly continuous.

Recurrent attacks of asthma, frequently associated with prolonged and severe vomiting, have also been observed during the past year.

Intracutaneous tests with milk, egg, beef, and chocolate elicited positive reactions.

The patient was put on a diet eliminating those foods to which he had shown a positive reaction. Complete freedom from vomiting ensued. The patient has made rapid gains in weight; the hemoglobin content of the blood has increased rapidly. During the year which has since elapsed, the child has not had any recurrence of the vomiting.

CASE 6.—P. K., a boy aged 8 years, had a history of hay fever since the age of 2 and of urticaria and angioneurotic edema since the age of 4 years.

He had received breast milk until 3 months of age. At that time, a supplementary formula containing cow's milk, water, and a carbohydrate was prescribed. Two hours after a small amount was ingested, he started to vomit and continued for over twenty-four hours.

This same formula of cow's milk was given for the second time three months later. Only about one teaspoonful was ingested. The remainder was refused. Again after two hours, he started to vomit and continued for twenty-four hours. Subsequent trials were made with other formulas containing cow's milk, with the same result. However, a formula substituting soybean flour for milk was easily tolerated.

At the age of 1 year, he was able to digest cow's milk without apparent effect.

A skin test with milk (1:10 dilution), made when we first observed this patient at 8 years of age, was negative.

COMMENT

Some of our observations on allergic children subject to recurrent vomiting have suggested a relationship between such vomiting and the ingestion of specific foods.

The detection of an offending substance was frequently difficult. The apparent regularity of vomiting after ingestion was often the sole clue for suspecting certain foods. Confirmation was achieved mainly through the use of trial and elimination diets. It was always important, however, to exclude organic disease and other functional disturbances.

Specific instances of apparent recovery following the elimination of offending foods from the diet are reported above. However, it is necessary to recognize that symptoms frequently subside spontaneously and that some of the successful therapeutic results achieved may have been due to a natural desensitization.

The relatively frequent occurrence of periodic vomiting among allergic children was impressive. Many of these children had a past history of repeated or protracted vomiting. Such vomiting occurring in early infancy had been diagnosed frequently as "pylorospasm," as pyloric stenosis, or as some other type of gastrointestinal disease.

SUMMARY

Recurrent or cyclic vomiting in children may be the gastrointestinal manifestation of food hypersensitiveness.

Six illustrative cases are presented wherein this syndrome apparently was precipitated by the ingestion of specific foods.

Particularly when they occur in children who manifest other allergic symptoms or are members of allergic families, such disturbances may be due to food sensitivity.

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485 Ocean Avenue

159 Midwood Street

A STUDY OF THE NUTRITIONAL AND PHYSICAL STATUS AND THE RESPONSE TO EXERCISE OF SIXTEEN NEGRO BOYS 13 TO 17 YEARS OF AGE

FREDERIC W. SCHLUTZ, M.D., MINERVA MORSE, PH.D.,
DONALD E. CASSELS, M.D., AND L. VIVIAN IOB, PH.D.
CHICAGO, ILL.

THE problems of what constitutes physical fitness in children, how it can be measured objectively, and how it may be improved have long been subjects of much interest and investigation, but as yet no entirely satisfactory answers have been found. Up to the present much of the emphasis has been placed upon measurements of nutritional status, cardiovascular rating, vital capacity, and tests of strength. The work of Dill[1] and his collaborators and of Robinson[2] suggests other lines of approach as, for example, a study of the blood changes and the rate of oxygen consumption during exercise. The introduction of the use of the blue dye, T-1824, by Gibson and Evans[3] as a satisfactory means of determining blood volume and the combining of this determination with that of "available fluid" volume through the simultaneous injection of sodium thiocyanate by Gregerson and Stewart[4] have opened up further lines of approach.

The present investigation was undertaken for the purpose of increasing our knowledge of physical fitness in the child by applying some of these methods to a study of the adolescent negro boy. The subjects of this study represent a group of volunteers contacted chiefly through the Y. M. C. A. and a neighborhood boys' club. About half of the group were Boy Scouts. Six of the group were definitely interested in competitive athletics, track, baseball, and swimming.

Since the age range of the boys covers the period of rapid adolescent growth, it has seemed wise to divide the boys into two age groups, group I including seven boys from 12 years 8 months to 15 years 7 months of age, and group II, nine boys from 16 years to 17 years 8 months. This has been especially desirable since it makes possible a comparison with two groups of white children of the same age range which Robinson[2] has studied so thoroughly in respect to physical fitness.

In the present study, the nutritional status of the subjects has been determined by anthropometric measurements and the calculation of the indices of weight, fat, and build as developed by McCloy,[5] and by determination of the creatinine index as defined in an earlier report by the authors.[6] The subjects were hospitalized for the purpose of collecting the twenty-four-hour urine specimen.

From the Department of Pediatrics, University of Chicago.

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The physical status of the subjects in the basal state has been determined by measurements of heart rate, blood pressure, total lung volume and its subdivisions, oxygen consumption, blood volume, and "available fluid" volume.

The physical capacity of the subject has been determined by the performance of the subject on the bicycle ergometer. His response to exercise of both a moderate and a vigorous character has been observed in the cardiovascular changes noted for four minutes after he stopped exercising and in the changes in the blood lactic acid and sugar and in the serum protein and phosphate of blood samples drawn during the twelfth minute of moderate exercise and five minutes after cessation of vigorous exercise.

DESCRIPTION OF AN EXPERIMENT

Each subject entered the hospital the evening before the day of the experiment and came to the laboratory in the morning without breakfast. After he had reclined fifteen minutes on a cot with one pillow under the head, the lung volume and its subdivisions were determined. Heart rate was palpated before and during the lung volume tests. Systolic and diastolic pressures were noted just after these tests. The lung tests lasted about one hour.

A 5 c.c. venous blood sample was next drawn to serve as a resting sample and as a control for the dye and thiocyanate samples. The drawing of the sample was followed by the injection through the same needle of 5 c.c. of a 0.15 per cent solution of the blue dye T-1824 and from 15 to 20 c.c. of a 5 per cent solution of sodium thiocyanate for the determination of blood volume and "available fluid" by the method of Gregerson and Stewart.[4] The drawing of 4 c.c. venous blood samples occurred at fifteen-minute intervals for one hour after the injection of the dye. From each sample a small portion was removed to a watch glass containing a small amount of heparin, and, after mixing, it was taken up in capillary hematocrit tubes and centrifuged twenty minutes at 2,000 revolutions per minute for cell volume determinations. From the initial resting sample a larger quantity was removed and mixed with heparin, and samples were measured out immediately for the determination of blood sugar and lactic acid. The remainder of each sample was allowed to clot, and the serum was removed later.

After all of the samples for the blood volume determination had been drawn, the subject was allowed to get up and was measured for weight, height, hip width, chest circumference, knee width, and fat of the front, back, abdomen, and hips by the methods described by McCloy.[7]

The exercise experiments followed next. Moderate exercise consisted in riding the bicycle ergometer for fifteen minutes at a fixed speed, which represented the performance of 1,700 foot pounds of work per minute. A 5 c.c. blood sample was drawn during the twelfth minute of exercise. Heart rates were recorded at fifteen-second consecutive intervals and systolic and diastolic pressures as frequently as possible for five minutes after the exercise period. After resting ten minutes, the subject began to ride as fast as possible. Under these conditions, the speed and the duration of the exercise varied with the individual. The exercise lasted from twenty seconds to four minutes. Heart rates and systolic and diastolic pressures were recorded as after moderate exercise. A venous blood sample was drawn five minutes after the subject had stopped riding.

The experiments were carried out in the summertime. The room temperature during exercise varied from 24.0 to 30.0° C., averaging 27.4° C. for all the experiments, and the relative humidity varied from 44 to 66 per cent, averaging 56.5 per cent.

METHODS

The procedure for determining the lung volume and its subdivisions followed that described by Robinson,[2] with the exception that in the residual air determinations the modification suggested by Lassen, Cournand, and Richards[8] was incorporated to correct for the lack of homogeneity of the gas mixture in the lung-spirometer system at the end of the determination. The apparatus used was a closed circuit spirometer of the Benedict type which had been modified as described by Robinson to reduce the dead space as much as possible. The capacity of the bell was about 6 L., the dead space of the apparatus, 2,260 c.c. The measurement of resting oxygen consumption constituted part of the residual air determination.

The procedure for the determination of blood volume and "available fluid" volume followed essentially that described by Gregerson and Stewart.[4] The concentrations of T-1824 in the serum were determined in the photoelectric colorimeter according to the method of Gibson and Evelyn.[9] Thiocyanate was determined in a microcolorimeter according to the method of Crandall and Anderson,[10] with the exception that the standard for comparison was made from thiocyanate-free serum to which had been added 0.5 c.c. of a standard thiocyanate solution (1 c.c. of the 5 per cent solution diluted to 500 c.c.) and 0.5 c.c. of 40 per cent trichloracetic acid. In calculating "available fluid," the thiocyanate concentration has been assumed to be the same as in the serum. The serum volume has been subtracted from the total thiocyanate containing fluid volume.

Blood samples in the resting state and after both moderate and vigorous exercise were analyzed for sugar, lactic acid, serum phosphate, and total nitrogen. Sugar was determined on 0.1 c.c. samples, according to the micromethod of Folin.[11] Lactic acid was determined on 0.5 c.c. samples by the modification of the Friedemann, Cotonio, and Shaffer[12] method described by Edwards.[13] Serum protein was estimated from total nitrogen analyses by means of the factor 6.25. Total nitrogen was determined on 0.1 c.c. samples by the micro-Kjeldahl method of Pregl.[14] Inorganic phosphate was determined on 0.2 c.c. samples by adapting the Fiske-Subbarow[15] method to use with the Evelyn photoelectric colorimeter.

NUTRITIONAL STATUS

Tables I and II give the nutritional rating of the subjects of this study. These boys are, on the average, shorter and lighter in weight than the white boys studied by Robinson. While such comparisons are of interest, it should be noted that, since the boys studied by Robinson came from a private school in Boston and therefore represent the product of a distinctly different socioeconomic environment, any differences between the two groups may not represent racial differences. It is interesting to note that one boy was taller than any in Robinson's group of the same age.

Because of the shorter stature and lighter body weight of the negro boys of this study, it is especially interesting to compare their weight with accepted standards. According to the Baldwin-Wood age-weight-height standards, these boys show an average weight index of 0.922 and 0.956 for the younger and older groups, respectively. When allowance is made for differences in skeletal build by the method of McCloy,[5] then the weights of the two groups appear quite normal, 0.99 and 0.98 where 1.00 represents the normal or average. Only three of the boys show a

weight index below the normal range allowed by McCloy, and these are the very tall boys of the group.

Three of the younger boys are unusually narrow in build, but the average index of build for the older group is but slightly less than normal. In many of the boys, especially in the older group, the index of fat is low. The majority of the boys are muscular but thin.

TABLE I

AGE, WEIGHT, AND HEIGHT OF THE SUBJECTS

GROUP NUMBER	NUMBER OF SUBJECTS	INVESTIGATOR	AGE IN YEARS		BODY WEIGHT (KG.)		BODY HEIGHT (CM.)	
			MEAN	EXTREMES	MEAN	EXTREMES	MEAN	EXTREMES
I	7	Authors	14.1	12.7-15.6	44.3	33.5-56.8	159.9	149-176
III	11	Robinson	14.1	13-15	55.8	41.7-67.4	165.7	155-171
II	9	Authors	16.9	16.0-17.7	57.4	53.8-63.3	171.5	161-180
IV	12	Robinson	17.4	16-19	68.4	55.1-88.0	179.2	172-190

TABLE II

NUTRITIONAL STATUS

GROUP NUMBER	SUBJECT	BALDWIN-WOOD WEIGHT RATING	INDEX OF BUILD (MC CLOY)	INDEX OF WEIGHT (MC CLOY)	INDEX OF FAT (MC CLOY)	CREATININE COEFFICIENT (MG. CREATININE PER KG.)	CREATININE INDEX*
I	J. F.	0.831	0.856	0.971	0.917	24.0	1.136
	O. H.	0.869	0.858	1.013	0.892	22.5	1.111
	H. M.	1.004	0.995	1.044	1.312	19.6	0.997
	T. S.	0.939	1.011	0.928	0.885	24.5	1.108
	T. R.	0.908	0.931	0.975	1.179	24.9	1.185
	W. B.	1.006	1.074	0.991	0.935	24.8	1.174
	H. N.	0.898	0.890	1.010	0.984	15.9	0.782
	Mean	0.922	0.945	0.990	1.015	22.3	1.070
II	H. G.	0.939	0.969	0.968	0.911	26.4	1.245
	A. B.	1.101	1.036	1.077	(0.919)	(5.8)	(0.304)
	L. B.	0.920	0.933	0.985	0.937	24.5	1.180
	S. Sc.	0.968	0.972	0.996	0.889	18.1	0.878
	N. W.	0.846	0.935	0.904	0.841	15.1	0.665
	H. H.	1.004	1.049	0.991	0.937	(6.3)	(0.305)
	S. So.	0.927	1.011	0.917	0.834	17.8	0.795
	J. M.	0.990	0.990	1.000	0.873	27.4	1.338
	C. H.	0.904	0.945	0.957	0.757	27.6	1.286
	Mean	0.956	0.982	0.977	0.878	22.4	1.055

*Defined as actual creatinine excretion divided by "normal" creatinine excretion, where "normal" creatinine excretion is assumed to be the "normal" weight of McCloy multiplied by 20.5, the normal creatinine excretion per kilogram of body weight as found by Talbot.[16]

The fact that the weight index is normal while the fat index for the majority of boys is low suggests that many of the boys are more muscular than the average. Such a supposition is supported by a high creatinine coefficient, especially in the younger boys. Half of the subjects gave a creatinine coefficient of from 24 to 27, and the group as a whole averaged 22.4, as compared with 20.5 which Talbot[16] found. In the case of the older boys, an occasional very low value suggests that the twenty-four-hour urine collection was sometimes incomplete. The two

TABLE III

LUNG VOLUME AND ITS SUBDIVISIONS*

GROUP NUMBER	NUMBER OF SUBJECTS	INVESTIGATOR	VITAL CAPACITY		RESERVE AIR		RESIDUAL AIR		TOTAL VOLUME	
			MEAN	EXTREMES	MEAN	EXTREMES	MEAN	EXTREMES	MEAN	EXTREMES
					Liters					
I	7	Authors	2.81	2.19-3.67	0.72	0.46-1.00	0.74	0.49-1.18	3.54	2.85-4.43
III	11	Robinson	3.71	2.93-5.07	0.82	0.49-1.28	0.95	0.70-1.52	4.67	3.63-6.15
II	9	Authors	3.72	3.32-4.22	0.99	0.84-1.23	0.87	0.49-1.78	4.59	4.00-5.69
IV	12	Robinson	4.95	4.12-5.98	1.18	0.89-1.54	1.30	0.97-1.75	6.25	5.23-7.58
					Cubic Centimeters Per Centimeter Body Height					
I	7	Authors	17.5	15-21	4.5	3-6	4.6	3-7	22.1	19-25
III	11	Robinson	22.4	19-25	5.0	3-7	5.7	4-9	28.2	23-35
II	9	Authors	21.7	19-23	5.8	5-7	5.1	3-10	26.7	24-28
IV	12	Robinson	27.4	23-32	6.6	5-9	7.3	5-9	35.1	32-41
					Cubic Centimeters Per Kilogram Body Weight					
I	7	Authors	63.7	55-79	16.1	11-20	17.2	10-30	80.8	71-98
III	11	Robinson	66.6	49-88	15.1	8-23	17.2	12-25	84.8	61-106
II	9	Authors	65.0	53-75	17.2	14-21	15.0	8-29	80.0	70-94
IV	12	Robinson	71.3	59-85	17.0	12-22	18.7	11-24	89.9	70-102
					Liters Per Square Meter Body Surface					
I	7	Authors	1.97	1.68-2.16	0.50	0.35-0.60	0.52	0.33-0.88	2.49	2.19-2.68
III	11	Robinson	2.31	1.85-2.77	0.51	0.30-0.74	0.59	0.44-0.86	2.90	2.30-3.36
II	9	Authors	2.23	1.91-2.47	0.59	0.48-0.73	0.52	0.29-1.01	2.75	2.52-3.23
IV	12	Robinson	2.65	2.32-2.95	0.63	0.51-0.84	0.70	0.46-0.93	3.35	2.92-3.74

*Volumes are expressed as gas saturated with H_2O at 37.0°C. and at the prevailing pressures.

very low values were omitted from the average. The creatinine index, calculated on the basis of normal creatinine output for children of the same skeletal build, shows unusually high values for some of the negro boys.

PHYSICAL STATUS

The total lung volume and its subdivisions, residual air, reserve air, and vital capacity, representing the sum of complemental and reserve air, are given in Table III. The volumes of all of the subdivisions increase with age, as shown by the average values for the two groups. The mean values for the boys of the present study are, in every case, less than those found by Robinson[2] for boys of the same age range. This is not surprising in view of the fact that the boys of this study are smaller. When referred to body height, weight, or surface, vital capacity and total lung volumes are still definitely smaller in the negro boys of this study. Since the reserve air volumes, when referred to body weight or surface, agree in both groups with those of Robinson's study, the smaller vital capacities of the boys of the present study may be attributed to smaller volumes of complemental air.

TABLE IV

RESIDUAL AIR VOLUMES* CALCULATED ACCORDING TO THE EQUATION OF CHRISTIE[17]

GROUP NUMBER	INVESTIGATOR	LITERS	C.C. PER KG. BODY WEIGHT	C.C. PER CM. BODY HEIGHT	LITERS PER SQ. M. BODY SURFACE
I	Authors	0.93	21.9	5.8	0.66
III	Robinson	0.95	17.2	5.7	0.59
II	Authors	1.16	20.1	6.7	0.70
IV	Robinson	1.30	18.7	7.3	0.70

*Volumes are expressed as gas saturated with H_2O at 37.0°C. and at the prevailing pressures.

The residual air volumes in this study have been calculated according to the equation of Lassen, Cournand, and Richards[8] which takes into account the percentage of nitrogen in the alveolar air at the time that the subject is connected to and disconnected from the closed system. In order to compare these volumes with those found by Robinson, who used the equation of Christie,[17] our data have also been calculated according to the latter equation. Residual air volumes appear somewhat greater when this equation is used. Table IV shows that, when the same method of calculation is used, the absolute volumes of our younger subjects are quite comparable to those of Robinson's study, while those of our older subjects are somewhat smaller. If the mean values are referred to body weight, both of our groups show greater volumes than those of Robinson's subjects, but if referred to body height or surface, they are fairly comparable. The younger group of our study shows a slightly higher residual air volume when referred to body surface, while the older group shows a slightly lower value when referred to body

height. Residual air volumes show greater individual variation than the other lung subdivisions. Part, at least, of this variation would seem to be due to experimental difficulties.

TABLE V

BASAL OXYGEN CONSUMPTION AND LUNG VENTILATION

FACTOR MEASURED		GROUP NUMBER	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION
Respirations per minute		I	14.5	7-17.5	± 4	26.2
		II	14.0	9-19	± 3	21.4
Oxygen consumption*	c.c./min.	I	205	179-238	± 24	11.4
		II	255	209-321	± 34	13.3
	c.c./kg./min.	I	4.70	4.01-5.56	± 0.57	12.1
		II	4.44	3.88-4.86	± 0.54	12.2
	c.c./m.²/min.	I	145	134-159	± 10	6.9
		II	152	130-190	± 18	11.8
	c.c. per Gm. creatinine	I	215	164-277	± 40	18.5
		II	210	147-322	± 63	30.0
	Comparison with Mayo Clinic standards	I	0.905	0.838-0.991	± 0.061	6.7
		II	0.985	0.828-1.249	± 0.124	12.6
	Comparison with Harris-Benedict standards	I	1.038	0.968-1.085	± 0.068	6.5
		II	1.108	0.943-1.393	± 0.135	12.2
Ventilation†	L./min.	I	6.64	4.61-8.89	± 1.46	22.0
		II	6.54	4.94-8.58	± 1.20	18.3
	c.c./kg./min.	I	152	104-228	± 38	24.9
		II	114	90-159	± 22	19.0
Tidal air†	c.c.	I	477	373-659	± 93	19.5
		II	479	399-632	± 76	15.9
	Percentage of vital capacity	I	18.1	12.4-25.7	± 5.4	29.8
		II	12.9	10.7-15.4	± 16	12.4

*Volumes are expressed at standard conditions.

†Volumes are expressed as gas saturated with water at 37.0° C. and at the prevailing pressures.

Table V gives the mean oxygen consumption of the subjects of this study in the resting state. Expressed as cubic centimeters per square meter of body surface, the oxygen consumption agrees in the case of the older group with the mean value found by Robinson for boys of that age range, 152 as compared with 151; but in the case of the younger group it is somewhat lower, 145 as compared with 157. The oxygen consumption for our younger group is also low when compared with the Mayo Foundation standards,[18] –9 per cent.

Talbot[19] has suggested that creatinine output may be used as a measure of metabolism in children. Expressed as cubic centimeters of oxygen consumed per gram of creatinine output, the younger group gives a slightly higher mean value than the older group, 215 as compared with 210. Wang[20] has shown that the ratio of calorie production to milligrams excreted declines slowly and steadily throughout childhood. Since very little data has appeared in the literature concerning boys of the age

range of this study, it is impossible to make accurate comparisons. Employing the equation of Talbot, calorie output = 0.669 creatinine excretion + 811, the calculated average twenty-four-hour calorie output for our two groups would be 1,463 and 1,662, respectively. The values found were 1,428 and 1,772. Since some of the values for creatinine excretion in the older group are questionably low, this may be taken as fairly good agreement.

TABLE VI

BLOOD AND FLUID VOLUMES

FACTOR MEASURED		GROUP NUMBER	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION
Cell volume	c.c./100 c.c.	I	42.7	38.2-46.3	± 3.0	7.0
		II	44.8	43.3-49.3	± 1.8	4.0
Serum volume	liters	I	2.00	1.39-2.55	± 0.47	23.3
		II	2.70	2.21-3.22	± 0.40	14.7
	c.c./kg.	I	45.0	39.5-56.8	± 6.2	13.7
		II	47.2	40.1-60.2	± 6.7	14.2
	c.c./cm.	I	12.4	9.1-15.8	± 2.4	19.5
		II	15.8	13.3-19.4	± 2.1	13.5
	L./sq.M.	I	1.40	1.14-1.65	± 0.22	15.4
		II	1.62	1.37-2.02	± 0.22	13.4
	c.c. per mg. creatinine	I	2.05	1.73-2.53	± 0.34	16.6
		II	2.33	1.66-3.02	± 0.52	22.1
Blood volume	liters	I	3.49	2.59-4.55	± 0.79	22.7
		II	4.89	4.05-5.77	± 0.67	13.8
	c.c./kg.	I	78.8	64.9-103.1	± 12.0	15.2
		II	85.3	72.4-104.5	± 11.7	13.7
	c.c./cm.	I	21.7	17.0-25.8	± 4.0	18.4
		II	28.5	23.5-35.2	± 3.7	13.0
	L./sq.M.	I	2.44	2.00-3.00	± 0.37	15.2
		II	2.93	2.47-3.66	± 0.38	13.0
	c.c. per mg. creatinine	I	3.58	3.07-4.59	± 0.63	17.6
		II	4.24	2.95-5.38	± 0.90	21.2
"Available fluid" volume	liters	I	11.33	8.19-16.89	± 3.08	27.1
		II	14.73	13.19-17.76	± 1.59	10.8
	c.c./kg.	I	253	204-297	± 33	13.2
		II	256	235-281	± 16	6.3
	c.c./cm.	I	70.2	54.8-95.9	± 14.3	20.4
		II	86.0	80.2-103.1	± 7.7	9.0
	L./sq.M.	I	7.88	6.30-9.93	± 1.26	16.0
		II	8.81	8.35-10.15	± 0.62	7.0
	c.c. per mg. creatinine	I	11.5	10.0-13.7	± 1.4	12.2
		II	12.6	8.9-17.9	± 3.4	27.0

Table VI gives the average blood and fluid volumes found for the subjects of this study. Cell volumes average 42.7 per cent for the younger group and 44.8 per cent for the older group. Serum volumes average 2.00 and 2.70 L. for the two groups, respectively, and blood volumes, 3.49 and 4.89 L. or 7.9 and 8.5 per cent of the body weight, respectively. "Available fluid" volumes average 11.3 and 14.7 liters for the two groups, respectively, or 25.3 and 25.6 per cent of the body weight.

TABLE VII

CORRELATION COEFFICIENTS

			GROUP I	GROUP II
"Available fluid"	vs.	Body surface	+0.8223	+0.8035
		Body weight	+0.7704	+0.5298
		Body height	+0.8098	+0.5377
		Chest circumference	+0.7734	+0.5750
		Index of weight	−0.6556	−0.3908
		Serum volume	+0.7660	+0.3342
		Blood volume	+0.7911	+0.2603
Serum volume	vs.	Body surface	+0.7361	+0.3830
		Body weight	+0.7250	+0.2769
		Body height	+0.6719	+0.3309
		Chest circumference	+0.6766	+0.2471
		Index of weight	−0.3798	−0.3200
Blood volume	vs.	Body surface	+0.7325	+0.3024
		Body weight	+0.6840	+0.2086
		Body height	+0.7306	+0.2665
		Chest circumference	+0.6370	+0.1630
		Index of weight	−0.4722	−0.2986
Lung volume	vs.	Body surface	+0.7710	+0.5356
		Body weight	+0.7212	+0.2603
		Body height	+0.7778	+0.6113
		Chest circumference	+0.7530	+0.4143
		Index of weight	−0.6849	−0.6092
		Fluid volume	+0.8464	+0.3664
		Serum volume	+0.7572	+0.3670

Coefficients have been calculated to show the degree of correlation between serum volume, blood volume, fluid volume, and a number of other body measurements. The results are shown in Table VII. Because of the small number of subjects in each group, these coefficients are valueless except as they may serve as tentative suggestions until more data may be secured. In the great majority of instances the younger group shows a higher degree of correlation between two given measurements than the older group. Serum, blood and fluid volumes show a slightly higher degree of correlation with body surface than with either body weight or height. "Available fluid" volume shows a higher degree of correlation with either body surface, weight, or height than do serum or blood volumes. Blood, serum, and fluid volumes show a high degree of correlation with total lung volume in the younger group. The coefficient of correlation between "available fluid" and either serum or blood volume is high for the younger group but quite low for the older group. The negative coefficients which occur whenever the index of weight is involved indicate that, for a given skeletal build, the child who weighs more tends to have a smaller lung volume and also smaller blood and "available fluid" volumes.

Heart rates in the resting state average the same for both age groups, 59 and 58, respectively. The mean value of 58 for the older group agrees with that found by Robinson for boys of the same age range, but the mean value of 59 for the younger group is much lower than the 75

found by Robinson. The older group in our study shows wider variation than the younger group.

Systolic pressure in the resting state averages 113 for the younger group and 121 for the older group; since diastolic pressure shows little difference between the two groups, 81 and 83, respectively, pulse pressure is lower for the younger group, 33 as compared with 38.

RESPONSE TO EXERCISE

The changes in heart rate and blood pressure measured within thirty seconds after both moderate and vigorous exercise on the bicycle ergometer are shown in Table VIII. After moderate exercise the heart rate increases to a mean rate of 129 beats per minute in the younger group and 109 beats per minute in the older group; after vigorous exercise the rates for the two groups are 151 and 137 beats per minute, respectively. The corresponding values found in Robinson's subjects are considerably higher, 162 and 147 for moderate and 197 and 193 for maximal effort. How much of this difference may be attributed to differences in actual work performed, how much to the type of work, bicycle riding as contrasted with running on a treadmill, and how much to the method of recording, palpation for fifteen seconds as contrasted with continuous tachometer recordings, can be determined in future experiments only by employing both methods on the same subject.

TABLE VIII

CARDIOVASCULAR RESPONSE TO EXERCISE

FACTOR MEASURED		GROUP NUMBER	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION
Heart rate (beats per minute)	Rest	I	59	53-67	± 4	6.8
		II	58	40-79	± 13	22.4
	Moderate work	I	129	112-148	± 16	12.5
		II	109	84-120	± 16	14.3
	Maximal work	I	151	112-168	± 19	12.4
		II	137	108-184	± 25	18.1
Systolic pressure (mm. Hg)	Rest	I	113	106-122	± 6	5.0
		II	121	108-136	± 9	7.9
	Moderate work	I	130	118-142	± 9	6.6
		II	136	122-156	± 9	6.9
	Maximal work	I	137	124-150	± 12	8.5
		II	152	130-170	± 12	7.8
Diastolic pressure (mm. Hg)	Rest	I	81	70-92	± 8	9.5
		II	83	78-92	± 4	5.2
	Moderate work	I	80	68-90	± 8	10.5
		II	78	68-88	± 7	8.5
	Maximal work	I	72	55-84	± 13	17.5
		II	73	56-88	± 12	15.8
Pulse pressure (mm. Hg)	Rest	I	33	24-44	± 8	24.2
		II	38	28-54	± 8	21.1
	Moderate work	I	50	40-60	± 7	14.0
		II	58	38-84	± 12	20.7
	Maximal work	I	65	44-95	± 19	29.3
		II	79	48-100	± 20	25.3

Systolic pressure rises to a mean of 130 in the younger subjects and 136 in the older subjects after moderate exercise, to 137 and 152 in corresponding groups after maximal exercise. Thus, the younger subjects appear to compensate for the increased oxygen demand to a greater degree by increased heart rate; the older subjects, by increased systolic pressure. Diastolic pressure shows approximately the same mean value for both groups and changes very little on the average during moderate exercise, but tends to decrease after vigorous exercise. In two subjects, however, diastolic pressure rises significantly after vigorous exercise. Pulse pressure increases more with vigorous than with moderate exercise.

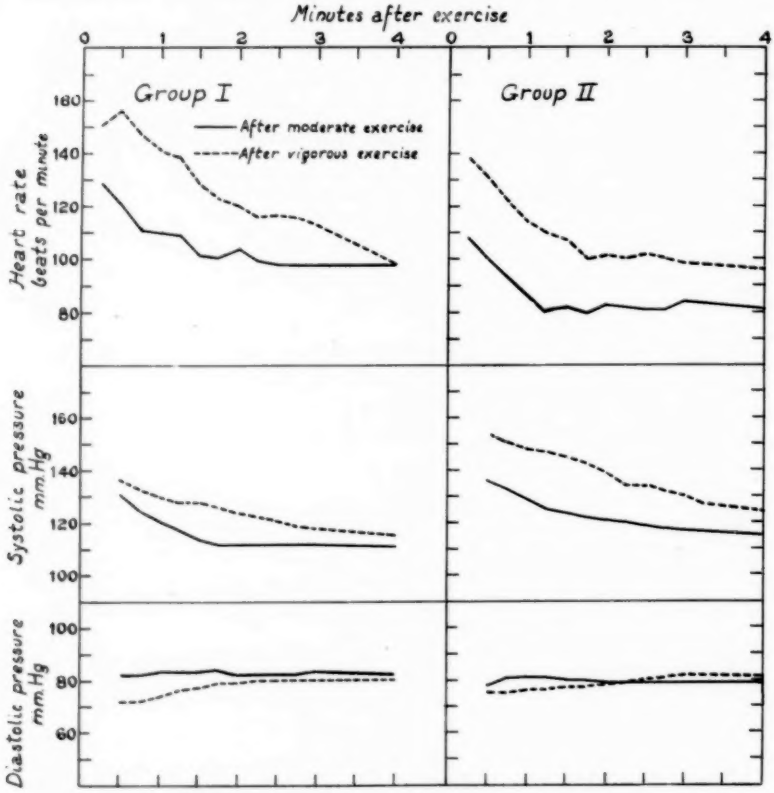

Fig. 1.—Cardiovascular changes during recovery from exercise.

The cardiovascular changes during the first four minutes of recovery are shown in Fig. 1. They are characterized by a slower recovery after vigorous exercise as compared with moderate exercise in both the younger and older groups. The greater lability of the younger boy is emphasized in that recovery after vigorous exercise is faster in the younger group.

TABLE IX

BLOOD CHANGES DURING EXERCISE

FACTOR MEASURED		GROUP NUMBER	MEAN	EXTREMES	STANDARD DEVIATION	COEFFICIENT OF VARIATION
Serum protein (Gm./L.)	Rest	I	80.8	69.3-91.1	± 7.9	9.8
		II	73.3	68.4-80.6	± 4.1	5.6
	Moderate work	I	85.2	75.9-93.8	± 7.4	8.7
		II	76.5	66.9-85.1	± 6.6	8.6
	Maximal work	I	85.8	73.1-96.9	± 12.0	14.0
		II	80.0	70.9-87.6	± 5.8	7.3
Blood lactate (mg./100 c.c.)	Rest	I	11.7	5.6-20.0	± 5.3	45.3
		II	8.0	5.4-11.9	± 2.5	31.2
	Moderate work	I	13.5	5.2-29.5	± 8.7	64.4
		II	9.0	3.5-16.9	± 3.9	43.3
	Maximal work	I	46.0	36.3-60.3	± 10.0	21.7
		II	47.8	12.5-97.2	± 7.4	15.5
Serum phosphate (mg./100 c.c.)	Rest	I	4.75	4.20-5.51	± 0.50	10.5
		II	4.44	3.19-5.22	± 0.59	13.3
	Moderate work	I	5.37	4.89-6.12	± 0.41	7.6
		II	4.81	3.81-5.45	± 0.51	10.6
	Maximal work	I	5.55	4.99-6.24	± 0.50	9.0
		II	5.03	3.85-5.75	± 0.62	12.3
Blood sugar (mg./100 c.c.)	Rest	I	92.4	88.1-97.6	± 3.6	3.9
		II	95.1	81.6-108.7	± 9.4	9.9
	Moderate work	I	90.9	85.5-98.0	± 4.8	5.3
		II	89.4	78.4-102.0	± 6.7	7.5
	Maximal work	I	98.6	87.7-108.7	± 8.5	8.6
		II	99.5	84.7-114.3	± 9.5	9.5

Table IX shows the changes which occur in the blood lactate and sugar and in the serum protein and phosphate during both moderate and vigorous exercise. Blood lactate in the present study shows very little change in concentration during the performance of the moderate fixed task. There is a significant small rise in only three subjects. The task selected did not prove difficult enough to test the physical fitness of the subjects by their lactic acid response. Following vigorous exercise, the blood lactate concentration varies from 36 to 60 mg. per cent in the younger group, and from 12 to 97 mg. per cent in the older group, an average of 46 and 48 mg. per cent for the two groups, respectively. These values are somewhat under the averages Robinson found for the two comparable groups, 62 and 66 mg. per cent, respectively. The work performed by the subjects in our study cannot always be described as maximal. It was limited by two factors, the difficulty of keeping the feet on the pedals during rapid riding and the fact that, after two of the boys had fainted following vigorous exercise, less encouragement was given them to try harder. The three boys who accomplished the most show blood lactate concentrations of 48, 54, and 97 mg. per cent.

Blood sugar changes during exercise in the present study are quite variable. During moderate exercise blood sugar increases slightly in three subjects and decreases slightly in ten subjects out of the fifteen on

whom we have data. The average of the group shows a slight decrease. During vigorous exercise blood sugar increases in nine and decreases in four out of the fifteen subjects on whom we have data. There is a small average increase. The highest blood sugar following vigorous exercise is only 114.3 mg. per cent. The boys in Robinson's study showed average blood sugar concentrations of 138 and 144 mg. per cent following vigorous running for the two age groups comparable to ours. The difference in type of exercise may be responsible for the difference in response.

The serum protein concentrations of our subjects in the resting and fasting state are unusually high compared with values found by Robinson in white boys of the same age range, mean values of 81 and 73 as compared with 65 and 66, respectively. This is especially true of the younger group in which four of the five subjects measured (samples on two of the boys were lost) give resting protein concentrations ranging from 79 to 95 Gm. per liter. It is interesting to note that three out of four negro boys in an earlier study also gave high serum protein concentrations of 75, 77, and 80 Gm. per liter, while the highest concentration shown by eight white children was 74 Gm. per liter.

During moderate exercise the protein concentration increases by an average of approximately 5 per cent in both groups, during vigorous exercise by 6 per cent in the younger group and by 9 per cent in the older group. The work accomplished by the older boys during vigorous exercise is considerably greater than that by the younger boys. The increase in protein concentration in the younger group is similar to that shown by a group of slightly younger children (11 to 13 years old),[6] which amounted to 4 per cent during moderate, and 6 per cent during vigorous exercise.

Serum phosphate increases during moderate exercise by an average of 13 and 8 per cent for the younger and older groups, respectively, and during vigorous exercise by 17 and 13 per cent, respectively. This increase is greater than that observed in our earlier study of children from 11 to 13 years of age, which amounted to only 4 per cent for moderate, and 5 per cent for vigorous exercise. The difference cannot be traced to racial differences since the four negro boys of the earlier study gave the same response as the white children. Whether the age of the group or the fact that the present study was conducted during hot summer weather, while the earlier study was conducted during the winter in a more moderately heated room, has any bearing upon the difference in response cannot be decided without further study.

SUMMARY

Sixteen negro boys, 13 to 17 years of age, have been studied as to nutritional status, physical status, including lung volume and its subdivisions, blood and "available fluid" volumes, basal oxygen consump-

tion, heart rate, and blood pressure, and response to exercise, including both cardiovascular and blood changes. For purposes of comparison, the boys have been divided into two age groups, one group including seven boys from 13 to 15 years of age, and the other, nine boys from 16 to 17 years of age.

The negro boys of this study are, on the average, 4 per cent shorter and 18 per cent lighter in weight than a group of white boys of the same age range but from a better socioeconomic environment who were studied by Robinson. When the weight of the negro boys is related to skeletal build, it compares well with the standards set up by McCloy. A low fat index and a normal weight index suggests that these boys tend to be more muscular than the average boy, a supposition which is supported by a high creatinine index.

The negro boys show smaller lung volumes than the white boys of Robinson's study, not only when expressed in absolute volumes, but also when referred to body weight, height, or surface. Expressed in liters per square meter of body surface, the vital capacity of the negro boys is 15 per cent lower than that of the white boys. Since the reserve air, expressed in liters per square meter of surface, is only 4 per cent lower, the smaller vital capacity is to be attributed to a smaller volume of complemental air. Residual air volumes, expressed in liters per square meter of surface, compare fairly well with those found in Robinson's study.

The average oxygen consumption of the boys of the present study, expressed in cubic centimeters per square meter of body surface, agrees with the average value found by Robinson in the case of the older boys, but in the case of the younger boys it is 8 per cent lower than Robinson's average and 9 per cent lower than the Mayo Clinic standards.

Blood volumes average 7.9 and 8.5 per cent of the body weight for the younger and the older boys, respectively. "Available fluid" volumes average 25.3 and 25.6 per cent of the body weight for the two age groups, respectively.

Resting heart rates average 59 and 58 for the younger and older boys, respectively; systolic pressure, 113 and 121, respectively; diastolic pressure, 81 and 83, respectively; and pulse pressure, therefore, 33 and 38, respectively.

In response to fifteen minutes of moderate work on a bicycle ergometer, the heart rate increases to an average of 129 beats per minute in the younger boys, and 109 beats per minute in the older boys; systolic pressure increases to 130 and 136 in the two groups, respectively, while diastolic pressure changes very little in most cases. In response to a short bout of vigorous exercise on the bicycle, the heart rate increases to 151 and 137 in the two groups respectively; systolic pressure increases to 137 and 152, respectively, while diastolic pressure decreases to 72 and 73, respectively.

The blood changes shown by the boys in this study in response to moderate exercise may be summarized as a concentration of the blood as evidenced by a 5 per cent increase in serum protein concentration, an increase in serum phosphate of 13 and 8 per cent in the younger and older groups, respectively, and very little change in blood sugar and lactate concentrations. The blood changes in response to vigorous exercise are greater, an increase in protein concentration of 6 and 9 per cent for the younger and older groups, respectively; an increase in serum phosphate of 17 and 13 per cent, respectively; a variable small change in blood sugar concentration; and an increase in blood lactate from a resting level of approximately 10 mg. per cent to an average of 47 mg. per cent. The lactic acid response shows wide variations among individuals.

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TUBERCULIN TESTING AS A CASE-FINDING PROCEDURE

PAUL S. PHELPS, M.D., VINCENT P. CENCI, M.D.,
AND ALICE LAWTON
HARTFORD, CONN.

THE opportunity for tuberculous infection of very young children is limited for the most part to familial contacts. With this thought in mind, a preliminary tuberculin-testing survey of Hartford children attending the medical well-child conferences conducted by the Visiting Nurse Association and the Board of Health was commenced in December, 1938. The primary purpose of this project was to determine whether the tuberculin testing of infants and preschool children was of sufficient value to warrant its routine use as a case-finding procedure.

The tests were performed by the medical director of the conferences. Purified protein derivative was used in the concentrations recommended by the National Tuberculosis Association. X-rays of positive reactors and of contacts were taken and read by the Director of the Bureau of Tuberculosis at the Board of Health Clinic. The home follow-up visits were made by representatives of the Visiting Nurse Association.

There were 229 white and 58 colored children, or a total of 287, tuberculin tested. Nineteen or 7 per cent of the total number gave positive reactions. Of the 229 white children, 12, or 5 per cent, gave positive reactions, and of the 58 colored children, 7, or 12 per cent, gave positive reactions. The higher percentage of positive reactions among the colored children was expected, as the tuberculosis death rate among negroes in Hartford in 1939 was 257.38 compared with a tuberculosis death rate among white people of 40.25 per 10,000 population. Also, the negro children came from that section of the city where such factors as poverty, ignorance, and disease are more prevalent. There were no four-plus reactions (with sloughing). One three-plus reaction (marked local reaction) occurred in a child who had been exposed to an open case of tuberculosis with positive sputum. Table I gives a summary of results.

Fifteen of the nineteen positive reactors were x-rayed. One child showed extensive pulmonary tuberculous infiltration of the secondary type. Three children were found to have x-ray evidence of the childhood type of tuberculosis with enlarged hilum lymph nodes.

Three of the families in which there were children with positive reactions were already registered with the tuberculosis service. There was a total of 65 reactor contacts. Forty-five, or 69 per cent, were examined. The presumptive source of infection was found for nine of

From the Bureau of Tuberculosis, and Maternal and Child Hygiene, Hartford Board of Health.

the reactors. One case was the presumptive source of infection for two children. As mentioned above, one open case with positive sputum was found. The remaining seven presumptive sources of infection showed x-ray evidence of disease ranging from pleural thickening to extensive fibrotic lesions.

TABLE I

RESULTS OF TUBERCULIN TESTS BY AGE AND COLOR

AGE (YR.)	NUMBER			POSITIVE TUBERCULIN TESTS					
				WHITE		COLORED		TOTAL	
	W	C	T	NO.	%	NO.	%	NO.	%
0-1	7	12	19	0	0	1	8	1	5
1-2	49	15	64	4	8	3	20	7	11
2-3	51	8	59	5	10	2	25	7	12
3-4	48	10	58	2	4	1	10	3	5
4-5	45	9	54	1	2	0	0	1	2
5-6	27	4	31	0	0	0	0	0	0
6-7	2	0	2	0	0	0	0	0	0
TOTAL	229	58	287	12	5	7	12	19	7

TABLE II

SUMMARY OF FINDINGS

Children tested	287	Familial contacts	65
Positive reactors	19	Contacts x-rayed	45
Per cent positive	7	Tuberculosis secondary cases†	8
Children x-rayed	15	Total secondary cases	9
Tuberculosis secondary cases*	1	Percentage secondary tuberculosis‡	15

*Child.
†Adults.
‡Of all cases x-rayed.

The number of children tuberculin tested and the number of familial contacts examined are too small for the results to be of statistical significance. The results suggest, however, that the examination of familial contacts of tuberculin positive children between the ages of six months and six years may be a valuable case-finding procedure. With this thought in mind, the tuberculin testing of children attending the Hartford Medical Well-Child Conferences will be continued until sufficient data have accumulated to prove or disprove its value as a routine procedure.

THE COMPLICATIONS OF MECKEL'S DIVERTICULUM IN INFANCY AND CHILDHOOD

With an Analysis of Fourteen Cases

Merrill W. Everhart, M.D.
New Orleans, La.

SOME portion of Meckel's diverticulum or some other remnant of the omphalomesenteric duct is found in from 2 to 4 per cent of all persons, and pathologic changes occur in from 25 to 30 per cent of the group in which the anomaly is present.[1] Its complications, therefore, cannot fairly be considered medical curiosities, as the increasing number of reports in the literature in the last ten years clearly proves. These complications constitute definite emergencies, particularly in pediatric practice. They are attended with a high mortality, and they must be borne constantly in mind if a reduction in the death rate is to be brought about.

Meckel's diverticulum usually takes the form of a blind pouch extending out from the free border of the ileum. It is from 1 to 3 inches in length, and has a broad base. Its location varies, but in children it is most often found from 12 to 18 inches from the ileocecal valve. Its wall is composed of all three layers which make up the bowel wall. It is lined with mucous membrane, the unusual characteristic of which is that it may contain cells structurally, and perhaps functionally, similar to the cells of gastric, duodenal, and pancreatic tissue.

It is necessary to understand the embryology of Meckel's diverticulum in order to appreciate the possible pathologic states which may arise from it. Early in fetal life there is a wide communication between the embryo and the yolk sac. By the fourth week the formerly broad connection is represented only by a narrow tubular structure known as the omphalomesenteric or vitelline duct. In the course of normal evolution the duct first becomes a mere fibrous cord between the umbilicus and the bowel, and then breaks, after which both ends atrophy and are absorbed.

If normal evolution does not occur, a number of abnormalities may develop, the special type depending upon the time at which the normal process is arrested. In general, they take three forms: (1) the connection between the umbilicus and the intestine may persist; (2) the umbilical portion of the duct may persist; (3) the intestinal portion of the duct may persist.

From the Department of Pediatrics of the School of Medicine of Louisiana State University and the pediatric services of the Charity Hospital of Louisiana at New Orleans.

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From the clinical point of view the most important complications which arise from the presence of Meckel's diverticulum may be divided into three groups—ulceration, inflammation, and various types of intestinal obstruction.[2]

1. Ulceration of the diverticulum or of the adjacent ileum, with or without perforation, is probably the result of the secretory activity of the heterotopic tissue. Bleeding from the intestinal tract is the outstanding symptom. It may take the form of occasional tarry or blood-tinged stools over a period of many months, or it may occur as a sudden hemorrhage which endangers life. The blood is bright red or dark, depending upon the rapidity of its expulsion from the rectum. Brennemann[3] has repeatedly stressed the diagnostic value of the fact that, when Meckel's diverticulum is present, the blood passed by rectum practically always contains clots, whereas the blood passed in the presence of intussusception and ileocolitis practically never does.

The abdominal pain associated with ulceration of Meckel's diverticulum is described by older children, who can relate their symptoms, as colicky or gnawing and as referred to the umbilicus. The picture changes, however, when perforation occurs. Then acute abdominal pain immediately ensues, attended with nausea, vomiting, generalized tenderness, and rigidity. Obstipation is frequently present, as is distention, although the latter is not usually marked.

2. Diverticulitis, in the opinion of many clinicians, cannot be differentiated from acute appendicitis. Wolfson and Clurman[4] do not accept this view. They describe the pain of diverticulitis as colicky, severe, and recurrent. Vomiting is fairly persistent and occurs several times a day. Distention is a prominent sign, appearing early and most often being localized to the lower half of the abdomen. Tenderness and rigidity are usually present and are localized about one-half inch below and to the right or the left of the umbilicus. This picture does not correspond in most respects to the picture of acute appendicitis, at least in its typical form.

Intestinal bleeding is occasionally associated with inflammation of the diverticulum, but it does not seem to be present as frequently as in association with ulceration. Perforation also can occur, but comes on more gradually than when it is associated with ulcer.

3. Intestinal obstruction is a mechanical complication which can assume several forms. In one type the intestine is strangled by a band which extends from the diverticulum to the umbilicus, the mesentery, or some adjacent viscus. In another type volvulus may occur. In still another type of obstruction the diverticulum serves as the starting point of an intussusception, and the classical signs of that condition are usually present. The onset is sudden and stormy. Acute abdominal pain, vomiting, and bleeding from the rectum are the chief symptoms, and a palpable, sausage-shaped mass usually develops promptly.

If the diverticulum has served as the starting point of an intussusception, or if obstruction occurs in association with inflammation or ulceration of the diverticulum, bleeding from the rectum is often observed. In this type of obstruction the blood is frequently clotted, and the picture, as a consequence, is somewhat confused. On the other hand, since surgery is indicated, regardless of whether the intussusception has originated in the diverticulum or is due to some other cause, failure to make a differential diagnosis is of no particular significance.

Hudson and Koplik[5] note that distention may be absent in intestinal obstruction associated with a diverticulum because the block is high in the intestinal tract. The picture of obstruction without distention is confusing, and valuable time may be lost if surgery is delayed while the exact diagnosis is being established.

A systematic survey of the files of the Department of Pathology of Charity Hospital of Louisiana for the eleven-year period ending July 1, 1939, with a more casual survey of the clinical files for a somewhat longer period, has revealed thirteen cases of diverticulum associated with complications in children under 12 years of age. The fourteenth case in this report is recorded through the courtesy of Dr. E. A. Socola, in whose private practice it occurred.

Eleven patients in this series were males and three were females, which bears out the generally reported sex incidence of 4:1. The age range was from 17 days to 11 years.

These fourteen cases fall naturally into two groups: inflammatory conditions, associated with perforation and peritonitis (five cases), and mechanical conditions causing intestinal obstruction (nine cases).

The five cases of diverticulitis all occurred in male children ranging in age from 4 to 9 years. Recovery ensued after the appropriate surgery in one of the two cases in which perforation was followed by a localized peritonitis with adhesions, with resulting secondary intestinal obstruction. Generalized peritonitis was present in the other three cases, two of which were fatal. Vomiting and abdominal pain were noted in all five cases, and bloody stools were present in two.

One case in this group is particularly instructive. A 7-year-old boy developed an acute abdominal condition which was diagnosed as acute appendicitis with peritonitis. At operation a generalized peritonitis was found, but the appendix, which was removed, did not seem sufficiently involved to be responsible for it. The mesenteric lymph glands were inflamed. No further exploration was undertaken, and six days later a gangrenous, perforated Meckel's diverticulum was found at autopsy. This case clearly suggests that a search for a possible Meckel's diverticulum should be made whenever the appendix cannot be incriminated as the cause of acute abdominal symptoms.

In six of the nine cases of intestinal obstruction, the diverticulum served as the advancing point of an intussusception. In four instances

TABLE I

MECKEL'S DIVERTICULUM WITH INTESTINAL OBSTRUCTION

Case 1	W. F., 17 days	Vomiting since birth. Stools not mentioned	Volvulus of ileum around band extending from Meckel's diverticulum to the umbilicus	Resection of ileum	Death
Case 2	W. F., 22 mo.	No history obtained. Died on admission	Distal fibrous end of Meckel's diverticulum attached to mesentery, causing strangulation of ileum	Autopsy findings	Death
Case 3	W. M., 11 yr.	Nausea and vomiting 24 hours, with abdominal pain and constipation	Fibrous cord extending from diverticulum to the mesentery, causing strangulation of ileum	Excision of diverticulum	Recovery
Case 4	W. M., 7 mo.	Abdominal pain, vomiting, bloody stools for 36 hours	Intussusception with diverticulum as the advancing point	Reduction of intussception	Recovery
Case 5	W. M., 14 mo.	Abdominal pain, vomiting, bloody stools for 48 hours	Intussusception with diverticulum as the advancing point	Reduction and excision of diverticulum	Recovery
Case 6	W. M., 23 mo.	Abdominal pain, vomiting, bloody stools for 48 hours	Intussusception with diverticulum as the advancing point	Reduction and excision of diverticulum	Death
Case 7	W. M., 3 yr.	Abdominal pain, vomiting, bloody stools for 72 hours	Intussusception with diverticulum as the advancing point	Enterostomy	Death
Case 8	W. M., 8 yr.	Abdominal pain, vomiting, bloody stools for 72 hours	Intussusception with diverticulum as the advancing point	Reduction and excision of diverticulum	Recovery
Case 9	W. F., 11 yr.	Abdominal pain, vomiting, and one bloody stool 24 hours	Intussusception with diverticulum as the advancing point	Reduction and diverticulostomy	Death

TABLE II

MECKEL'S DIVERTICULUM WITH PERFORATION

Case 10	W. M., 4 yr.	Abdominal pain and vomiting for 72 hours. Stools not mentioned	Perforated gangrenous Meckel's diverticulum. Generalized peritonitis	Excision of diverticulum	Recovery
Case 11	W. M., 4 yr.	Abdominal pain and vomiting for 5 days. Constipation 2 days. Stools not mentioned first three days of illness.	Perforated gangrenous Meckel's diverticulum. Generalized peritonitis	Excision of diverticulum	Death
Case 12	C. M., 7 yr.	Abdominal pain and vomiting for 2 days. Bloody stools not mentioned	Generalized peritonitis found at operation. The appendix was removed. Six days later autopsy revealed a perforated gangrenous Meckel's diverticulum	Appendectomy	Death
Case 13	W. M., 8 yr.	Abdominal pain and vomiting for 1½ days. Bloody stools	Gangrenous diverticulum. Localized peritonitis with adhesions causing intestinal obstruction	Freeing of adhesions and excision of diverticulum	Recovery
Case 14	W. M., 9 yr.	Abdominal pain and vomiting with one bloody stool 3 days	Gangrenous diverticulum. Localized peritonitis with adhesions causing intestinal obstruction	Freeing of adhesions and excision of diverticulum	Death

the diverticulum was excised after the intussusception had been reduced. The same procedure was employed in the fifth case and was followed by enterostomy. In the sixth case the child's condition precluded any more radical surgery than reduction of the intussusception. In several of these cases operation was resorted to only after attempts at non-surgical reduction had failed. Three of the six patients died.

In one of the three remaining cases the cause of the obstruction was a fibrous cord which extended from the diverticulum to the umbilicus and caused a volvulus of the ileum; resection was undertaken, but the child, who was 17 days old, died immediately after it was completed.

In the other two cases the obstruction was caused by a similar cord which extended from the diverticulum to the mesentery. One of the children recovered after excision of the diverticulum; the other died before surgery could be undertaken.

TABLE III

SUMMARY OF FOURTEEN CASES OF MECKEL'S DIVERTICULUM

Male	11
Female	3
	14
Under 2 yr.	5
2– 6 yr.	3
6– 9 yr.	3
9–12 yr.	3
	14
Cases showing hemorrhage	
Associated with diverticulitis	2
Associated with intussusception	6
	8
Cases of diverticulitis	
With localized peritonitis	2
With generalized peritonitis	3
	5
Cases of obstruction	
Fibrous band from diverticulum to umbilicus	1
Fibrous band from diverticulum to mesentery	2
Intussusception with diverticulum as advancing point	6
	9
Deaths	
Associated with diverticulitis	3
Associated with intussusception	3
Associated with other obstruction	2
	8
Mortality rate	
Under 2 years of age	60%
From 2 to 12 years of age	55.5%
For entire group	57%

SUMMARY AND CONCLUSIONS

The fourteen cases of Meckel's diverticulum presented in this paper fall into two groups, inflammatory states with perforation (five cases) and intestinal obstruction (nine cases).

Eleven cases occurred in males and three in females, all of the latter cases being in the intestinal obstruction group.

The history of the passage of blood by rectum, in association with vague abdominal pain, is so frequent in young children with Meckel's diverticulum that it should at once make one suspect the diagnosis. Bloody stools were definitely stated to have been present in eight of the cases reported herewith.

The eight deaths in the fourteen cases resulted in the high mortality of 57 per cent.

Temporizing or medical treatment is not safe when Meckel's diverticulum has been diagnosed or is suspected, since perforation is a possibility with either ulceration or inflammatory changes. The contents of the ileum are highly infectious as compared with the contents of the upper intestinal tract, and the prognosis is therefore decidedly worse when perforation occurs.

A careful search should be made for a possible Meckel's diverticulum whenever the abdomen is opened on a diagnosis of acute appendicitis and whenever the state of the appendix does not explain adequately the symptoms or the findings of a generalized peritonitis.

Since Meckel's diverticulum is not infrequently associated with intussusception in infants and young children, this single consideration should be enough to condemn the widespread routine medical practice of attempting closed reduction of the intussusception by means of a barium enema or by the introduction of water under high pressure. Even when the attempt is believed to have been successful, the findings at autopsy frequently prove that it has not been. Furthermore, since ulceration or inflammatory changes may be present in a diverticulum which is the advancing point of an intussusception, this method of treatment can easily result in rupture of the friable walls of the diverticulum, or of the bowel itself.

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EXPERIENCE WITH BENZEDRINE SULFATE IN THE MANAGEMENT OF OBESITY IN CHILDREN

RALPH H. KUNSTADTER, M.D.
CHICAGO, ILL.

IN A previous communication[1] it was emphasized that, regardless of the underlying cause of obesity, dietary restriction is of paramount importance. Whether obesity is a result of an hereditary or constitutional factor, hyperalimentation or an endocrine disturbance, a state of overnutrition exists for the particular obese child. In other words, there is an excess of intake over the caloric requirement.

The majority of obese children have a healthy or excessive appetite. The child enjoys eating, and his will power, and frequently that of his parents, is poor. Frequently, the appetite is a question of satiation, a factor that becomes important in dealing with the psychologic approach to the problem of obesity.

Bruch[2] recently has studied the physiologic and psychologic aspects of the food intake of obese children and agrees that the real problem of children lies in the unwillingness or inability of the children to adhere to the prescribed diet. In her study, Bruch emphasizes the relationship of emotional adjustment and environment to eating and food habits. Overprotection on the part of the parents resulting in immature behavior in eating habits, eating as an outlet for unsatisfied desires, plays an important role. Myerson[3, 4] also emphasizes the social habits and psychologic influence upon appetite, and his syndrome of "anhedonia" explains the vicarious appetite of many obese persons. This syndrome consists in a "diminution even to the point of disappearance or antagonism of satisfactions normally obtained from life activities and in a loss or distortion of the appetites and desires." Such persons constantly nibble, eating candy, nuts, and so forth, as a nervous habit.

Newburgh[5] also believes that obesity is, in the main, the outcome of a perverted habit and that there is a "dulling of the acuity of the sensations, a weak will, and a pleasure-seeking outlook on life."

It is our belief also that the emotional or psychologic aspects of treating the obese patient are important, and in order to have a prescribed reducing diet adhered to, we must give them careful consideration. The parents as well as the patient must cooperate fully.

In the particular group that forms the basis of this report, another important factor must be mentioned, and that is the racial one. Many of these children are of the Jewish race, a race that is known for its

From the Children's Endocrine Clinic, Michael Reese Hospital.

relatively high incidence of obesity. This may be due to hereditary or constitutional factors and to the fact that many parents are oversolicitous, particularly with reference to their children's eating habits. Many erroneously believe that a fat child is a healthy child.

We have always attempted to get full cooperation from the parents so that they might encourage their children in the difficult task of adhering to a reducing diet. To the older children we have tried to explain the purpose of the diet, particularly with respect to health and a presentable appearance.

Despite the use of a bulky high protein diet[1] and thyroid extract for many patients, appreciable weight loss was the exception rather than the rule. In fact, the use of thyroid extract frequently increased the appetite, and weight gain was not unusual unless the drug was increased to the point of tolerance.

The major problem is, therefore, How can the appetite be controlled so that a prescribed reducing diet will be adhered to?

Recently, Lesses and Myerson[4] found that when benzedrine sulfate was administered to various psychotic adult patients, frequently there resulted a decrease in the appetite, a disappearance of the feeling of fatigue, and a beneficial influence on the state of mind. With the decrease in appetite, there resulted voluntary dietary restriction, and weight loss occurred in many patients.

Since Lesses and Myerson's observation, there have been several reports on the use of benzedrine sulfate in the management of obesity in adults, with favorable results.[6] In view of the fact that the obesity of adults frequently begins in childhood because of faulty food habits, and because cooperation by children is difficult to obtain, a therapeutic measure that might be of some help in the management of this problem should be gratefully received by the pediatrician.

It is true that a large number of preadolescent obese children outgrow their obesity spontaneously, due to an apparent self-regulation of their neuroendocrine system which usually occurs during the transition from childhood to adulthood; nevertheless, there are a large proportion of obese children who do not outgrow their obesity and require medical aid. The work of Lesses and Myerson quoted above induced us to treat obesity in children with benzedrine.*

MATERIAL FOR STUDY

This study comprises a group of thirty obese children ranging from 2½ to 16 years of age, from both clinic and private practice (see Table I). There were fourteen males and sixteen females. These patients were chosen without consideration of the etiological factor. Some of the males had received hormone treatment for hypogenitalism and cryptorchidism without influencing their obesity. Twenty-five of the thirty

*Supplied by Smith, Kline and French Laboratories.

had received, for a period of from one month to over one year, in addition to a reducing diet, thyroid extract (at various times) without causing a reduction in weight. All patients had been observed for long periods before the institution of benzedrine therapy, so that a "control period" was observed for all patients. All received a complete physical examination with special diagnostic laboratory work when indicated. The basal metabolic rate was observed before and during treatment in ten patients, and particular attention was paid to the effect of benzedrine upon pulse and blood pressure. Untoward reactions were given serious consideration because of reports relating to toxicity and unpleasant reactions following administration of the drug. All patients were seen at regular intervals of one week at the onset of treatment and no longer than three-week intervals at any time. Whenever the dose was increased, the patient was seen the following week.

TABLE I

BENZEDRINE TREATMENT OF OBESITY

CASE NO.	AGE (YR.)	SEX	HEIGHT (IN.)	WEIGHT (LB.)	POUNDS OVER-WEIGHT*	MAXIMUM DAILY DOSE (MG.)	DURATION OF TREATMENT (WK.)	WEIGHT CHANGE (LB.)	AVERAGE WEEKLY WEIGHT LOSS
1	12½	M	62¾	165½	58½	15	19	−23¼	1.22
2	13	M	64	151½	40½	15	12	−11	0.90
3	14	M	63¾	168½	55½	50	21	− 4	0.19
4	15	F	63½	192	73	25	27	−41	1.51
5	2½	F	39½	57½	22½	10	3	+ ½	(0.00)
6	9	F	52½	89	14	20	13	− 8	0.61
7	11½	M	66	183	64	10	3	− 3	1.00
8	16	M	69	185	42	30	24	− 4	0.16
9	12	M	63½	151	42	15	6	− 3½	0.58
10	11	M	54½	90	20	10	4	0	(0.00)
11	16	F	61	145½	33½	30	23	−10	0.43
12	4½	F	45	63½	21½	10	½	− 4	(7.84)
13	9½	F	52	85½	21½	15	6	− 4½	0.75
14	10½	M	60½	119	24	15	7	−10	1.43
15	10	M	59	99	12	10	½	0	(0.00)
16	13½	F	60	139½	38½	10	2	0	(0.00)
17	10	M	60	135½	44½	20	8	0	0.00
18	13	F	63	160	46	30	20	−21	1.05
19	14	F	63½	135	22	20	10	−10	1.00
20	15	M	60¾	125	25	20	5	− 5	1.00
21	16	F	62½	176½	59½	20	6	0	0.00
22	9	F	52	100	39	25	12	0	0.00
23	14	F	59¾	158½	57½	30	13	−22½	1.73
24	11	F	60	118½	23½	25	8	− 8½	1.06
25	13	M	61	127½	30½	25	4	− 8½	2.12
26	14	M	69	207½	70½	20	10	−17½	1.75
27	8	M	47½	71½	18½	15	8	− ½	0.06
28	14½	F	62	157	44	20	13	−12	0.92
29	15	F	61	151½	43½	20	15	−16½	1.10
30	10	F	58	141	57	15	18	−20½	1.14
Average of 26 Cases									0.831

*Baldwin and Wood.

Dosage.—The dose of benzedrine chosen for these patients was an individual proposition. No optimal effective dose for the management of

obesity in children has as yet been established. For the treatment of the obese adult, Rosenberg[6a] and Rosenthal and Solomon[6d] prescribed from 10 to 30 mg. daily for most patients. Rosenberg started with 7.5 mg. before breakfast and 2.5 mg. before lunch, and this 10-mg. dosage was increased by 2.5 mg. weekly until the proper amounts were determined for each individual patient.

At the beginning of our study, small doses proportional to the adult dose were administered cautiously. Individual doses of 1.25 and 2.5 mg. administered two and three times daily usually were without effect upon appetite and body weight. Thereafter, 5 mg. was chosen as the initial dose regardless of the age (youngest child treated, 2½ years old). It was increased gradually to what was considered an optimal effective dose according to the effect upon appetite and weight loss. The drug was administered either twice or three times daily, before breakfast and lunch, and after school if a third dose was given. An evening dose was avoided so that it would not interfere with sleep. The maximum daily dose prescribed for any one patient was 50 mg. to a 14-year-old male weighing 168.5 pounds (Case 3). The majority received a daily dose of from 10 to 30 mg.

According to the amount of drug suggested for the treatment of psychotic adults with and without obesity and nonpsychotic obese persons, the optimal effective dose for children in our experience was surprisingly high. Many of the children took amounts of the drug as large as usually prescribed for adults without showing untoward symptoms. For this reason an optimal effective dose cannot be calculated on the basis of either age or body weight.

It is generally agreed that a definite tolerance to the drug not uncommonly occurs so that, to be effective, the dose must frequently be increased. However, most reports state that it is seldom necessary to go beyond 50 mg. a day, and the optimal daily dose for the average adult patient usually does not exceed 20 mg. The Council of Pharmacy and Chemistry of the A. M. A.,[7] in recommending the adult dose of benzedrine for various clinical uses, suggests that the initial dose should be from 2.5 to 10 mg., and increased up to not more than 20 mg. three times daily in order to produce a therapeutic response.

RESULTS

Effect of Benzedrine Upon Body Weight.—Benzedrine sulfate was administered to thirty patients. However, there were four who received the drug regularly for less than three weeks, a period too brief to evaluate properly the effect of the medication.

Case 5: Drug taken irregularly during a three-week period. Mother forced food because the child refused to eat. Gain of ½ pound.

Case 12: Drug discontinued after five days because of marked anorexia and untoward symptoms. Loss of 4 pounds.

Case 15: Drug discontinued on second day because of untoward symptoms.

Case 16: Drug discontinued after two weeks because of untoward symptoms. Weight unchanged.

Twenty-six patients received the drug for periods of from three weeks to six months. The greatest weight loss occurred during the first two weeks, with an average of approximately 2.5 pounds per patient. Rosenthal and Solomon[6d] also found that the greatest weight loss occurred in the first weeks of treatment, with an average individual weight loss of 1.55 pounds during the first four weeks. The average weekly weight loss of our twenty-six patients was 0.831 pounds, almost identical with that of Rosenthal and Solomon's patients (0.81 pounds). Rosenberg[6a] found a greater weekly weight loss averaging 2.4 pounds for ninety patients.

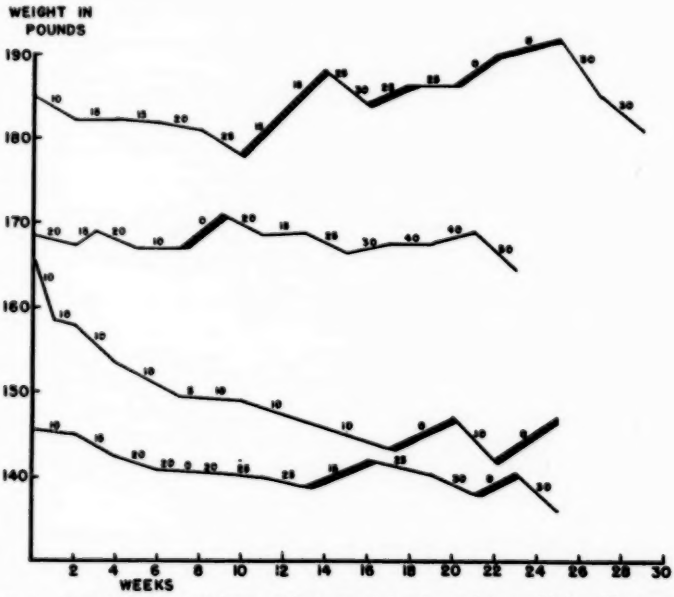

Fig. 1.—Weight curves of four patients receiving benzedrine sulfate. The numbers indicate the daily dosage of the drug in milligrams. Heavy lines indicate gain in weight following withdrawal of the drug or reduction of the dose.

The 0.831 pound average weekly weight loss of our patients may be of greater significance if we compare this figure to that obtained by Rosenthal and Solomon. All of our patients had either failed to lose or had continued to gain weight on a prescribed reducing diet with and without thyroid extract previous to benzedrine therapy, whereas

their patients lost an average of 0.11 pounds per week on a reducing diet without benzedrine.

Our experience with respect to alternate administration and withdrawal of the drug was similar to that of Rosenthal and Solomon.[6d] Fig. 1 shows the rise in the weight curve following withdrawal and reduction of the dose of drug, and a fall in the weight curve following resumption of therapy and increase of the dose. Although this is the usual result, there are some patients who hold their weight following withdrawal of the drug. This is particularly true for those patients who have taken the drug for a considerable length of time and have lost a good deal of weight.

Effect Upon Basal Metabolic Rate.—The basal metabolic rate of ten patients was determined before institution of benzedrine therapy and during the period of maximum dosage. There was very little change in the basal metabolic rate during treatment. Only four patients, Cases 3, 4, 8, and 18, who received 50, 25, 30, and 25 mg. per day, respectively, showed an insignificant increase of between 3 and 6 per cent. These patients were among those who received larger doses of the drug. These results agree with those of Rosenthal and Solomon,[6d] who found no evidence of increased metabolic rate in their patients. It is generally believed that any increase in basal metabolism is due to a mild increase in oxygen consumption, due to an involuntary increase in muscular activity after administration of the drug.

Effect Upon Pulse and Blood Pressure.—The pulse rate and blood pressure were taken on all patients after a ten-minute rest lying down before institution of therapy and at regular intervals thereafter. Unless there is a decided change in either the pulse rate or blood pressure during treatment, it is difficult to evaluate the effect of the drug, as we must realize that small fluctuations of from 2 to 5 mm. of mercury occur normally in children following various activities.

The pressor effect of therapeutic doses of benzedrine administered to our children apparently was variable.

In our group of thirty obese patients, a slight fall in systolic blood pressure occurred in nine of twenty-five patients on whom determinations were taken regularly, a slight elevation occurred in four patients, and no significant change was observed in twelve of the patients. Two patients developed a marked bradycardia.

Case 3, with an initial pulse rate of 68 and blood pressure of 102/70, developed a bradycardia of 48 without significant change in the blood pressure while taking from 10 to 20 mg. of benzedrine daily. However, following an increase to 50 mg., the pulse rose to 80 and the blood pressure to 112/78.

Case 8, with an initial pulse rate of 72 and blood pressure of 124/88, developed a bradycardia of 44 with a fall in blood pressure to 110/70

while taking 25 mg. both of which continued lower than the initial determination during the remainder of treatment on 30 mg.

Heart block was suspected in both of these patients. However, electrocardiography did not substantiate this suspicion.

The effects of benzedrine upon the cardiovascular system in our patients are consistent with observations made on a large number of adult patients by other authors. It is a consensus of opinion in the literature that benzedrine in single oral doses of less than 20 mg. has little pressor effect on blood pressure. In fact, Franke[8] reports a slight fall in both systolic and diastolic pressure in seven of eight cases receiving 5 mg. A fall may also occur with 10 mg.,[9] but slight increases are frequent.[10] An increase of systolic pressure greater than 20 mg. has not been reported except in rare instances of lability or idiosynerasy. With doses of 20 mg., sixty-five to eighty-nine subjects[10, 11] had a rise averaging 17 mm. systolic and 11 mm. diastolic. Six subjects were not influenced, and in eighteen there was a fall averaging 12 mm. systolic and 7 mm. diastolic. With larger doses of from 30 to 80 mg., there is a more pronounced pressor effect. The average rise noted in twenty-two subjects receiving 30 mg. orally was 22 mm. systolic and 15 mm. diastolic.[10, 11b, 12a, 12b, 12c] Other authors, however, report little increase in blood pressure with similar and larger doses. As occurred in many of our patients, when benzedrine sulfate is administered over long periods, tolerance to the pressor effect often develops,[11c 13] and in obese persons, a fall of blood pressure frequently occurs.[3, 6a]

TABLE II

UNTOWARD SYMPTOMS (12 PATIENTS, 40 PER CENT)

SYMPTOM	NUMBER	PERCENTAGE
Dizziness	5	16.7
Abdominal pain	5	16.7
Headache	3	10.0
Insomnia	3	10.0
Nausea or vomiting	3	10.0
Nervousness	2	6.7
Talking in sleep	1	3.0
Fainting	1	3.0
Substernal pain	1	3.0
Pains in extremities	1	3.0
Frequency of urination	1	3.0

Untoward Symptoms.—Twelve, or 40 per cent, of the thirty patients showed untoward symptoms during treatment. Table II shows the symptoms in the order of their frequency. Treatment was discontinued by only four patients, Cases 7, 12, 15, and 16, because of unfavorable reactions.

Case 7: Dose 10 mg. Drug discontinued by mother after three weeks because of severe pains in stomach, dizziness, and nervousness.

Case 12: Dose 10 mg. Drug discontinued by mother after five days because of severe abdominal cramps, headaches, dizziness, and complete anorexia.

Case 15: Dose 10 mg. Drug discontinued by mother on second day because of abdominal cramps, vomiting, and severe headaches.

Case 16: Dose 10 mg. Drug discontinued after two weeks because of sticking pains in arms and feet, substernal oppression, nervousness, dizziness, and two fainting spells.

Most unfavorable symptoms occurred at the onset of treatment, usually during the first two days, and these were not severe, disappearing as tolerance to the drug developed and only occasionally recurring on a gradual increase of the dose. Some authors have suggested the administration of sedatives with the benzedrine to ward off unpleasant reactions. However, it was felt in this study that nothing should be given so that no unfavorable symptoms would be masked. It is interesting that none of the patients (Cases 3, 4, 11, 18, 22, 23, and 25) receiving larger doses of 50, 25, 30, 30, 25, 30, and 25 mg., respectively, experienced unpleasant symptoms. Rosenthal and Solomon[6d] in their entire series found no untoward effects which could be ascribed to benzedrine, except for occasional gastric upset when the drug was taken on an empty stomach; Rosenberg[6a] mentions only minor complaints. Elimination of an evening dose usually prevents insomnia.

It is interesting that one of our patients (Case 10) developed avitaminosis B, cheilitis, sore tongue, and intermittent diarrhea while taking benzedrine. In an attempt to cause weight loss, his mother had eliminated all cereals, including bread, from his diet for several months previous to benzedrine therapy. Consequently the vitamin deficiency could not be attributed solely to the benzedrine which he took for only four weeks. This case is mentioned, however, to warn against the occurrence of vitamin deficiency in any patient on a strict reducing diet.

DISCUSSION

The results obtained by treating a group of thirty obese children with benzedrine sulfate indicate that the drug is of definite value, but, nevertheless, it is not a panacea for all cases.

All patients were observed for long periods before the administration of benzedrine. During the observation periods, a reducing diet was prescribed and a large number of patients also received thyroid extract. Because permanent weight reduction was not accomplished by any of these patients, they were selected for benzedrine therapy. It is believed that such a group offers a better test for the efficacy of benzedrine than a group who had not been subjected to dietary restriction and thyroid extract.

Loss of appetite with subsequent decrease of food intake was the primary reason for loss of weight. Patients offered this explanation, frequently without questioning, and many mothers stated that their children refused to eat and many times "skipped" meals. The anorexia was so great at times that the parents became alarmed. In two instances the parents refused to continue treatment (Cases 5 and 12).

An improvement in the state of mind, increasing the will power to resist food, was at times a contributing factor, but certainly was not an outstanding result of the drug. This reaction probably assumes greater importance with respect to psychotic persons such as those treated by Lesses and Myerson.[4]

Appetite is a complex problem. In the newborn infant most probably appetite does not exist as yet, and the craving for food is due to hunger sensation only. As man or animal grows up, appetite develops on the basis of pleasant experience with certain foods. Usually appetite is secondary to hunger, i.e., the sensation of hunger appears first, and the selection of food is directed by appetite. It is not uncommon, however, that the memory of a pleasant food will per se produce the sensation of hunger. We know that in certain people a perversion of hunger occurs during which the frequent or constant cravings of appetite regulate the intake of food rather than the regularly recurring periods of hunger, which, in most normal persons, have been conditioned to the three daily meal periods. Lack of training to regular feeding times and to a discipline of not eating between meals, as well as pathologic trends, predispose to this perversion. Appetite is a function of memory. No appetite center is known to exist. Ravenous hunger, associated with lesions of the anterior lobes of the brain, probably has no relation to appetite.[15]

The effects of benzedrine on body weight may be due to various factors: increase of general body motility and reflex activity; decrease of gastric and intestinal motility, and diminished absorption of food;[16] suppression of digestive secretion, particularly of appetite secretion, and diminished digestion and utilization of foods.[17]

Some of the patients who appeared languid or lazy before administration of benzedrine became more active physically and developed more "pep," apparently due to increased muscular activity and not as a result of increased metabolism.[6d]

In addition to loss of appetite and reduction of the food intake, increased water excretion may be a contributory factor in weight loss. Rosenthal and Solomon[6d] mention a patient who lost weight gradually on a diet of from 2,000 to 2,300 calories with benzedrine sulfate, but rapidly gained weight with the same number of calories following withdrawal of the drug. The only way that they could explain the phenomenon was on the basis of increased elimination of water. They were unable to check water balance on their patients and, therefore,

could not confirm their belief. All of our patients were ambulatory, and therefore it was impossible for us to study the water balance accurately. In our previous study of obese children,[1] we also considered water retention a factor in obesity and in many instances prescribed diuretics in addition to a high protein low salt reducing diet.

During the course of treatment benzedrine was withdrawn or the dose was decreased in several patients with the purpose of controlling the actual efficacy of the drug. Following this, the appetite usually increased and gain in weight occurred. Fig. 1 shows this response. On resuming benzedrine or on increasing the dose, there usually occurred a definite weight loss until drug tolerance was established.

In view of the fact that appetite frequently returns and weight increase takes place after withdrawal of the drug, benzedrine sulfate alone is not the sole answer to managing obese patients. During the period of treatment, attempts should be made to adjust abnormal psychologic and socio-economic conditions so that, following the withdrawal of the drug, weight reduction may be maintained.

It is believed that a maximum dose of from 10 to 30 mg. daily of benzedrine sulfate will produce a desirable response in most instances if the drug is to react favorably at all. Doses larger than 30 mg. were used only when tolerance to the drug resulted. The drug was increased in Case 3 from 30 to 50 mg. when the weight remained stationary, and after five weeks on the latter dose, the weight again remained stationary.

In view of the fact that untoward symptoms are usually slight and transitory and easily controlled by reducing the dose, the drug may be administered without trepidation in most instances. However, treatment should always be under the control of a physician.

In many of the cases reported, the blood was examined for toxic changes. No significant variations in the blood picture were observed.

Because of the report by Friedenberg[14] relative to addiction to benzedrine sulfate, we were careful to observe the effects upon the patients on withdrawal of the drug. In our group there was no actual craving for the drug, although a few patients stated that they believed they could do better with their diet if the drug was taken.

SUMMARY AND CONCLUSIONS

Benzedrine sulfate was administered to thirty obese children between 2½ and 16 years of age. These children were selected after they failed to lose weight on a prescribed reducing diet.

Many patients, in addition to a reducing diet, had received thyroid extract.

The average weekly weight loss of twenty-six patients who received continuous treatment for over two weeks was 0.831 pounds per week.

The greatest weight loss occurred during the first two weeks of treatment.

There was little or no variation in the basal metabolic rate while under benzedrine treatment.

The effect of benzedrine upon pulse rate and blood pressure was variable. A slight fall in systolic blood pressure occurred in nine patients, a slight elevation in four, and no significant change in four of the twenty-five patients on whom determinations were taken regularly. Two patients developed a marked bradycardia.

Forty per cent of the patients experienced unpleasant reactions at the onset of treatment. However, withdrawal of the drug was necessary in only four instances because of severe reactions.

The optimal effective dose of benzedrine for obese children apparently is between 10 and 30 mg. daily.

Weight loss was primarily due to loss of appetite with subsequent decrease of food intake. Improvement in the state of mind, with increase of will power, was probably a contributory factor.

Withdrawal of the drug or decrease in the dose usually resulted in a return of appetite and an increase in weight.

Tolerance to the drug developed frequently, requiring gradual increase in the dose.

Although benzedrine sulfate is frequently an effective adjunct in the management of obesity in children, it is not a panacea. Social and psychologic adjustments, including improvement of the food habits, should be attempted during the course of treatment so that, following withdrawal of the drug, excessive food intake with regain of weight loss will not occur.

The author wishes to express his gratitude for the helpful suggestions and criticisms of Dr. H. Necheles, Director of the Department of Gastro-Intestinal Research, Nelson Morris Institute, Michael Reese Hospital.

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104 South Michigan Boulevard

DURATION OF DIPHTHERIA IMMUNITY

A Follow-up Study

Amos Christie, M.D.
San Francisco, Calif.

IMMUNITY to diphtheria following the use of various antigenic materials may not be as lasting as we had previously hoped. Recent studies have substantiated the earlier suggestions of Frazer, Halpern, Brandon, Park and Jones[1, 2, 3, 4] on this point. Schwartz and Janney[5] retested 145 children six or seven years after they had received toxoid and found that "22 per cent showed a reversal to a positive Schick test." Hillman and Linde[6] compiled "data concerning 180 children who had been Schick tested again (one to five years) after having been negative once to the Schick reaction." The percentage of reversals from negative to positive was 25.5 per cent.

It is the purpose of this study to add to this accumulating evidence which implies that the general practitioner, the school health officer, and the pediatrician must not take too much for granted as to the percentage of Schick immunity in the children under their supervision.

In conjunction with the Well Baby Clinic of the University of California Out-Patient Department, there has been for some years an Immunization Clinic to which after the infant is six months of age it is referred for routine immunization against smallpox and diphtheria. Through the courtesy of several pharmaceutical houses manufacturing biological products, it has been possible in this clinic to evaluate the effectiveness of some of the commercially available antigenic materials. Because of a relatively stable clinic population we could follow a considerable number of the children for a sufficient length of time to chart the ultimate duration of this immunity.

The present study is an evaluation of seven different antigenic preparations used in the production of diphtheria immunity. In most cases the immunizing materials were used according to the directions of the supplying company. It was realized very early that one week was too short an interval between doses, but that period was used to complete as many cases as possible. Likewise we knew that four to six weeks, or even three months, was too short an interval to make Schick tests after immunization, but the short interval was used as in the case of the immunizing doses, in order to give as many patients complete courses as possible.

In other words, we realize that it is impossible to compare one material with another because of the differences in amounts used, in

From the Department of Pediatrics, University of California Medical School.
Eli Lilly & Co., and E. R. Squibb & Sons furnished the material used.

TABLE I

RESULTS OF IMMUNIZATION, 1932-1934, WITH VARIOUS COMMERCIAL PREPARATIONS AND FOLLOW-UP, 1939-1940, BY RETESTING (SCHICK)

COMMERCIAL PREPARATIONS	YEAR GIVEN	DOSAGE*		INTERVAL BETWEEN T.A.T. OR TOXOID AND SCHICK	TOTAL NO. SCHICK TESTS DONE	SCHICK TESTS PERCENTAGE		INTERVAL SINCE T.A.T. OR TOXOID (YR.)	NO. AND PERCENTAGE OF PREVIOUS NEGATIVE SCHICK REACTORS RE-CHECKED 1939-1940	
		NO.				NEG.	POS.		NEG.	POS.
A. T.A.T (sheep serum)	July '30 to Oct. '31	1:1 c.c. 2:1 c.c. 3:1 c.c.	Toxin contained 0.22 c.c. per L+ dose	3 mo.	52	77	23	9	8-88%	1-12%
B. Toxoid with alum†	Dec. '31 to June '32	1:1 c.c. 2:1 c.c. 3:1 c.c.	5-6 Lf. units c.c.	3 mo.	49	96	4	7	12-85%	2-15%
C. Toxoid with alum†	Aug. '32 to Apr. '34	1:½ c.c. 2:½ c.c.	10+ Lf. units c.c.	1 mo.	167	91	9	5½ to 7	23-52%	21-48%
D. Toxoid without alum	Aug. '32 to Apr. '34	1:½ c.c. 2:1 c.c.	10+ Lf. units c.c.	1 mo.	87	87	13	5½ to 7	8-50%	8-50%
E. Toxoid with alum precipitated	Apr. '34 to Dec. '34	1:½ c.c.	12 Lf. units c.c.	1 mo.	49	90	10	5	6-46%	7-54%
F. Toxoid with alum precipitated	Dec. '34 to Apr. '36	1:½ c.c.	44 Lf. units c.c.	6 wk.	101	95	5	4	18-75%	6-25%
G. Toxoid without alum	Dec. '34 to Apr. '36	1:1 c.c. 2:1 c.c.	30 Lf. units c.c.	6 wk.	94	94	6	4	18-75%	6-25%

*All repeated doses were given at one-week intervals.
†0.5 per cent alum added. Experimental material not now commercially available.

methods of administration, in the flocculating unitage, and in intervals between immunization and Schick testing. Likewise it is impossible to compare the results with those obtained in private practice. Nevertheless, these discrepancies do not minimize the lesson to be learned from an accumulation of such data. Schick tests were performed and read according to the standard procedures set up by the Committee on Immunization Procedures of the American Academy of Pediatrics.

RESULTS

Table I reveals that between July, 1930, and October, 1931, toxin antitoxin (commercial preparation A) was used on 52 children. Three 1 c.c. doses of the material were given at weekly intervals. After three months the Schick tests made revealed that 77 per cent of the children were Schick negative. It was possible to retest nine of this Schick-negative group nine years later and eight were still negative.

Commercial preparation B was also given in three 1 c.c. doses a week apart. This was toxoid to which 0.5 per cent of alum had been added and contained a flocculating unitage of five to six units per cubic centimeter. In three months 93 per cent of the children were Schick negative. It was possible to retest 14 of this group seven years later and 12 (85 per cent) were still negative.

Essentially the same material except for a higher flocculating unitage (commercial preparation C) was given in two 0.5 c.c. doses one week apart and 91 per cent of the children were Schick negative, and surprisingly enough after five and one-half to seven years only 52 per cent were Schick negative. Of this negative group 48 per cent had reverted to a Schick positive reaction.

Between August, 1932, and April, 1934, plain toxoid was given with an initial dose of 0.5 c.c. followed in one week by 1.0 c.c. (commercial preparation D). After one month 87 per cent of the group had a negative Schick reaction. However, after five and one-half to seven years it was possible to retest 16 of these negative Schick reactors, and one half of the group had become Schick positive.

Commercial preparation E was equally poor in maintaining Schick immunity. After five years with this "one dose" alum-precipitated toxoid 90 per cent of the children were immunized, but only 46 per cent of the Schick negative reactors remained so. Another commercial preparation (F) given in the same manner (one dose of 0.5 c.c.) but with a flocculating unitage three and one-half times that of commercial preparation E, held up much better and 75 per cent of the known negative Schick reactors were still negative after four years.

Two 1 c.c. doses of plain toxoid one week apart (commercial preparation G) produced 94 per cent of negative Schick reactors in six weeks and after four years 75 per cent of this group of children still had negative tests.

SUMMARY AND CONCLUSIONS

A follow-up study to test the duration of Schick immunity is reported. Various commercially available antigenic materials are evaluated. Depending on the type of material, amounts given, and the period between injections and the Schick test, 77 to 95 per cent of the group were found to have negative Schick tests in four to twelve weeks. After a four to nine year follow-up period, 46 to 88 per cent of these known Schick negative reactors were found to have continued negative; 12 to 54 per cent had reverted to positive.

This study strongly suggests that all children immunized in the first year of life should be Schick tested again on admission to school. Schick-positive reactors should then be given a stimulating dose of toxoid.

The writer is grateful to Miss Dorothy Keane, head nurse in the Children's Clinic, who was responsible for the return of the various groups for testing, and to Dr. William J. Vasquez for his assistance on a grant from N.Y.A. funds.

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THE RELATION OF VITAMIN D INTAKE TO THE AGE OF THE INFANT AT THE TIME OF ERUPTION OF THE FIRST DECIDUOUS INCISOR

THOMAS D. SPEIDEL, D.D.S., AND GENEVIEVE STEARNS, PH.D.
IOWA CITY, IOWA

NUTRITION is generally conceded to influence growth, including the time of dental eruption. However, specific information as to possible relationships between dietary constituents and the time of dentition is not available. Hence, it was thought that the dentition records of infants with carefully controlled dietary intakes might offer some information concerning the effect of nutrition on the time of tooth eruption.

Dental records of healthy infants from the "well-babies" ward of the Pediatrics Department of the State University of Iowa Children's Hospital were available for this project. The infants were of the white race and from parents of the lower socio-economic levels. These infants were brought into the ward at a very early age, usually under 2 weeks of age, for nutrition studies. The duration of the infants' stay in the ward ranged from a few weeks to fifteen months, depending upon circumstances such as opportunity for adoption and parental desires. Infants younger than 18 weeks at the time they left the ward were not included in this study. Fifty-one infants were in the ward until after their first tooth erupted, and eleven remained until after all eight of their deciduous incisors appeared.

The date of the appearance of each tooth was a part of the daily records kept for each infant by the ward nurses. The day on which any of the incisal or occlusal portion of a tooth appeared through the gum was recorded as the date of eruption.

All infants were given a good, high calorie diet consisting of whole milk with 5 per cent additional carbohydrate. Other dietary additions were 1 oz. of orange juice daily to infants under 4 months of age, 2 oz. to older infants, an egg yolk at 4 months, sieved vegetables at 5 months, and sieved fruits at 6 months. The only major variable in the diets of these infants was the amount of supplementary vitamin D intake.

Twenty-two infants received from 300 to 400 U.S.P. units of supplementary vitamin D daily, an amount which promotes optimum linear growth in infancy.[1, 2] Seventeen infants received from 135 to 270 units, and six were given over 1,800 units daily. The feeding of these diets was begun when the infants were less than 2 weeks of age and was continued at least until the age of from 24 to 28 weeks was reached.

From the Department of Orthodontics, College of Dentistry, and the Department of Pediatrics, College of Medicine, State University of Iowa.

The infants who received from 300 to 400 units daily were maintained on that regimen throughout their stay in the ward. The D intakes of those who were given the low or high amounts of vitamin D were shifted to a more desirable amount at approximately 6 months of age when it became evident that their general growth was inferior to the 300- to 400-unit group. No infant developed any roentgenologic or clinical evidence of rickets during the study.

Under these circumstances, it would appear that the effect of vitamin D intake on eruption of teeth would be most evident on the teeth erupting during or closest to the period of experimental feeding. Hence, the ages at which the first lower deciduous central incisor erupted in these groups of infants were compared in order to determine whether or not these dietary variations influenced dental eruption.

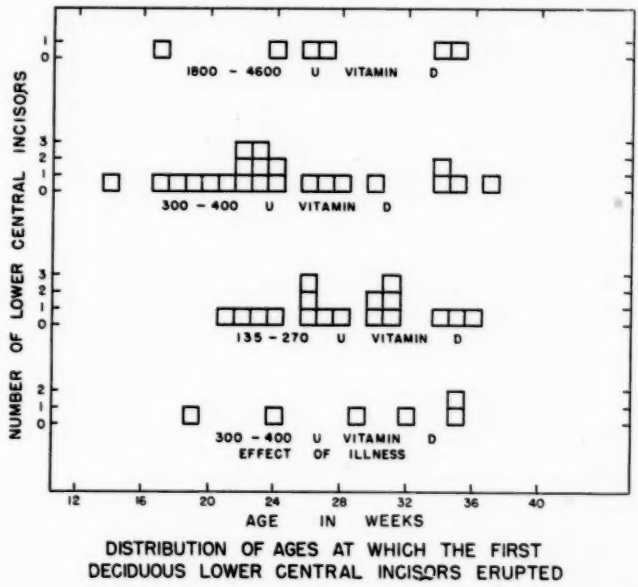

Chart 1.

Chart 1 presents the distribution of the eruption times of the first lower deciduous central incisor of the infants in the three experimental groups, and also those of infants who received the optimum diet but suffered either severe acute or mild chronic illnesses during their first six months of life. The number of infants is indicated on the ordinates, each square representing an infant and his first lower deciduous central incisor. It is evident that the first lower central incisors of the healthy infants who received from 300 to 400 units of vitamin D tend to erupt at a somewhat earlier age than those of the other groups of infants. However, the eruptive age ranges of all groups overlap, and there arises

the question of whether the apparent differences are real or are due to chance distribution in the relatively small groups. Statistical analysis (Table I) of the only two groups large enough for such treatment, the 135- to 270-unit and the 300- to 400-unit groups, shows a high probability that the difference between their mean ages of eruption, 28.29 weeks and 24.68 weeks, respectively, is a statistically significant or real difference.* Thus, these data indicate that one of the effects of a low vitamin D intake is a tendency toward delayed eruption of the first lower deciduous central incisor.

TABLE I

ERUPTION OF THE FIRST LOWER DECIDUOUS CENTRAL INCISOR OF HEALTHY INFANTS GIVEN LOW, INTERMEDIATE, AND HIGH AMOUNTS OF VITAMIN D AND INFANTS GIVEN INTERMEDIATE AMOUNTS OF VITAMIN D BUT HAVING SEVERE ACUTE OR MILD CHRONIC ILLNESSES

	DIET WITH 135 TO 270 UNITS VITAMIN D	DIET WITH 300 TO 400 UNITS VITAMIN D	DIET WITH OVER 1,800 UNITS VITAMIN D	DIET WITH 300 TO 400 UNITS VITAMIN D—SEVERE ACUTE OR MILD CHRONIC ILLNESSES
Number of infants	17	22	6	6
Mean age at eruption of first lower deciduous central incisor	28.29 wk.	24.68 wk.	27.16 wk.	29.0 wk.
Standard deviation	4.37	6.02		
"t" test	2.03			

The effect of a high vitamin D intake is less clear, although the mean age of incisor eruption, 27.16 weeks, unreliable for a group this small, shows a tendency for later eruption.

Since there may be some question as to whether early or late eruption of teeth is more nearly normal, the data from infants who were given the 300- to 400-unit intake but were subject to illnesses are included in this report. Although only six infants comprise this group, their mean age of incisor eruption, 29.0 weeks, shows a tendency toward later eruption. If this may be taken as a true indication that illnesses delay eruption of teeth, it would seem that the earlier eruption age may be accepted as more nearly normal.

The effect of variation in vitamin D intake on the eruption of these teeth is similar to its effect on linear growth and mineral retention of these infants. Jeans and Stearns[4] recently showed that infants ingesting from 300 to 400 units of vitamin D daily had better than average linear growth and mineral retention; those receiving from 135 to 270 units grew at average rate; those receiving over 1,800 units were above

*The value of "t" is 2.03, which is significant at the 5 per cent level for 37 degrees of freedom. This implies that a value of "t" as large as 2.03 would be found by chance not more than 5 per cent of the time when comparing samples of this size.[3]

average during the first five or six months of life, after which their progress was definitely slower than average.

DISCUSSION

Relatively few studies available in the literature present data concerning tooth eruption and nutrition. Ledé,[5] in 1924, published average ages of eruption of deciduous teeth of four groups of French infants. The artificially fed infants, the nurslings of wet nurses, and the infants of wet nurses with nurslings erupted their deciduous teeth later than the infants of wet nurses without other nurslings.

Boas,[6] in 1927, presented the eruption time of deciduous teeth of infants in the New York City Home for Hebrew Infants. The definite retardation of these infants' dentition, when compared with any of the usual eruption tables, was attributed to the poor condition of the infants when they entered the Home. It is probable that nutrition was an influence in this situation.

Gesell and Thompson,[7] in 1938, reported anthropometric norms, including the time of dental eruption, from an outpatient study of infant growth. The infants were a carefully selected, homogeneous group whose birth history, physical status, parentage, and socio-economic status were within specified limits. While specific information as to the nutrition of these infants is not available, it is probable that parents who would cooperate with such a study would also offer their infants better than average care and diets. Fifteen male infants had an average of one erupted tooth at 28 weeks of age, and eighteen female infants reached that average between 28 and 32 weeks of age. While these data are not strictly comparable with the average eruption ages of the Iowa infants, it may be noted that the ages at which Gesell's infants averaged one erupted tooth are very near the average age at eruption of the first tooth of the Iowa infants who received from 135 to 270 units of supplementary vitamin D.

A study of the effect of increased vitamin B intake on growth and nutrition of infants, reported by Poole, Hamil, Cooley, and Macy[8] in 1937, included data as to the time of eruption of deciduous teeth. The infants were well babies from indigent and near indigent families of Detroit. Approximately two-thirds of the groups of infants were white and one-third were negro. Food was provided for the infants, and close medical and nursing supervision were exercised. The diets of all of the infants included from 250 to 600 units of vitamin D. Fifty-nine infants received additional vitamin B, and forty-three infants, the control group, received no supplementary vitamin B. The intake of vitamin B was the only dietary difference between the groups. The age at appearance of the first tooth and the average number of teeth present at four-week intervals throughout the first year were recorded. There was very little difference between the dentition of these two groups of

infants. The average age at appearance of the first tooth was 31.6 weeks for the infants receiving vitamin B and 32.3 weeks for the control group of infants. These mean ages at eruption of the first tooth are from seven to eight weeks later than the mean age of the group of Iowa infants who received from 300 to 400 units of vitamin D (Table II). However, the vitamin D intake of these infants and the Iowa infants may not be exactly comparable, since the diet of the inpatient Iowa infants could be very strictly controlled. It is possible that influences other than diet may contribute to the differences between these infants. The incidence of illness was much lower for the Iowa infants. Also, while all of the infants were from the lower economic levels, the Iowa group of infants were all of the white race.

TABLE II

COMPARISON OF AVERAGE AGES AT ERUPTION OF THE FIRST DECIDUOUS TOOTH

	POOLE AND MACY STUDY*		MAY AND WYGANT STUDY* IRRADIATED, EVAPORATED MILK	IOWA INFANTS, WHITE; 135 TO 270 UNITS VITAMIN D	IOWA INFANTS, WHITE; 300 TO 400 UNITS VITAMIN D
	VITAMIN B GROUP	CONTROL GROUP			
Number of infants	59	43	31	17	22
Mean age at eruption	31.6 wk.	32.3 wk.	28.85 wk.	28.23 wk.	24.54 wk.
S. D.			7.55	4.35	5.78
Range	18.7 to 48.5 wk.	14.4 to 48.5 wk.	13.0 to 52.0 wk.	21.0 to 36.0 wk.	14.0 to 35.0 wk.

*Included white and negro infants.

A study of the value of irradiated evaporated milk in the prevention of rickets, by May and Wygant[9] in 1939, included data concerning the eruption of deciduous teeth. It was possible to determine, from their data, the ages at eruption of the first tooth of thirty-one infants who received irradiated, evaporated milk. None of these infants had roentgenographic symptoms of rickets. The average age at which the first tooth appeared in these infants was 28.85 weeks, approximately the same average age as that observed in the Iowa babies who received from 135 to 270 units of vitamin D, and more than four weeks later than the mean age of the Iowa infants who received from 300 to 400 units of vitamin D.

The possible influence of the infants' sex on the time of dental eruption has not been discussed. The infants were grouped according to sex only by Gesell and Thompson.[7] Their data showed that the males and females had the same average number of erupted teeth at the twentieth and twenty-fourth weeks, but thereafter the males' averages were higher. Thus, it may be possible that varying proportions of males and females in the various groups may account for some of the

variations. Less than 25 per cent of the infants of the Iowa groups were female; the percentages in the remaining groups were unpublished.

Although these groups of infants are not strictly comparable in all respects, it is clear that the mean age at eruption of the first tooth of the Iowa group given from 300 to 400 units of vitamin D daily is lower than the mean ages of all other groups shown in Table II. At least two of these groups of infants received less than 270 units of vitamin D daily. The degree of dietary control of the two Iowa groups was constant; the only alterations in diet were the vitamin D intakes. Therefore, the variation in mean age at eruption is ascribed to differences in vitamin D level.

SUMMARY

The ages at eruption of the first deciduous lower central incisor of groups of healthy infants with carefully controlled diets having relatively low, intermediate, and high amounts of supplementary vitamin D were compared.

The incisors of twenty-two infants given the intermediate vitamin D intake, from 300 to 400 units daily, showed the earliest mean age at eruption, 24.68 weeks. The incisors of seventeen infants with a low vitamin D intake, from 135 to 270 units daily, were delayed in their eruption, appearing at a mean age of 28.29 weeks. Incisors of six infants with a high vitamin D intake, over 1,800 units daily, also seemed delayed in their eruption, appearing at a mean age of 27.16 weeks; however, this is less conclusive because of the small number of infants in this group.

In an effort to determine whether early or late eruption is more nearly normal, the dental eruption data of six infants who had the 300- to 400-unit intake but who were subject to illnesses were presented. Although the group is small, the mean age of incisor eruption, 29.0 weeks, seemed to indicate that illness delays tooth eruption and that the earlier eruption age is more nearly normal.

The response of dental eruption to variation in vitamin D intake tends to parallel the responses of linear growth and mineral retention to the same influence during infancy.

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TERATOMA OF THE PINEAL BODY*

JESSE R. GERSTLEY, M.D., JACOB KASANIN, M.D.,†
AND ELIZABETH LOWENHAUPT, M.D.
CHICAGO, ILL.

THE subject of teratoma of the pineal body has been reviewed recently by Bochner and Searff, who remarked on the rarity of this tumor. These authors found reports of thirteen proved cases and they added a fourteenth. To alleviate the confusion concerning the terminology of the group of embryonal tumors, these authors subdivided this set of neoplasms, defining a teratoma as an embryonal tumor derived from all three primitive germ layers. Most authors draw no exact distinction between the terms teratoma, dermoid, and teratoid, and from McLean's summary of twenty-five cases of pineal teratoma several tumors of the first two groups must be subtracted. To the fourteen teratomas listed by Bochner and Searff, three may be added: one reported by Allen and Lovell (Case 7), one by Dandy, and one by Bailey, Buchanan, and Bucy (Case 91).

Symptoms in pineal tumors are of two types. Mechanical signs of increased intracranial pressure, which may be intermittent due to the valvelike action of the free-lying tumor in the third ventricle, may be unaccompanied by focal signs, or pressure on the quadrigeminal bodies may produce the only localizing signs. Endocrine disturbances may be absent or may produce the striking picture of macrogenitosomia praecox. This syndrome was present in nine of the patients with embryonal tumors and in ten of those with more numerous simple and mixed tumors reviewed by Bochner and Searff. In a recent review of patients with pineal tumors who showed macrogenitosomia praecox, Bing, Globus, and Simon offered their thesis as to the mechanical role of the pineal body in the production of this much discussed syndrome. An extensive bibliography was included by these authors as well as by Bochner and Searff.

The following example of this rare tumor is reported because of its interest to students of pediatrics, neuropsychiatry, endocrinology, and pathology. This is the eighteenth teratoma of the pineal body reported in the literature.

H. A., a boy of 11 years, entered Sarah Morris Hospital on Dec. 6, 1938, complaining of vomiting and loss of 9 pounds of weight during the past two weeks. He was the younger of two children of an apparently healthy family. Birth and development had been entirely normal until the age of 10½ years. He had always been an alert student at school and was a leader among the boys of his age at summer camp.

From the Sarah Morris Hospital for Children and the Departments of Psychiatry and Pathology of the Michael Reese Hospital.

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†Mount Zion Hospital, San Francisco.

In retrospect the date of onset of his illness was set at May, 1938, when on a 100-mile automobile trip he stopped frequently to urinate and drank about a gallon of water. About this time nocturia developed and also an abnormal craving for candy and ice cream. In July he went to camp and here polydipsia and especially polyuria became acute problems. At this time he weighed 84 pounds. Upon returning home in August, he often napped after lunch, contrary to previous custom. These naps became longer so that he slept all afternoon, returning to bed tired and drowsy after a short period of play. The mother noted that the boy seemed less alert, had no appetite, and was losing weight. However, he attended school all fall, maintaining his previous high scholarship. No concern was aroused until two weeks prior to admission, when projectile vomiting began, usually following the evening meal and resulting in a weight loss of 9 pounds. The family physician was consulted, and finding no gastrointestinal basis for the vomiting, he advised hospitalization. During the previous five months the boy's voice had become very deep and a moderate growth of pubic hair had appeared.

Physical examination on admission showed a well-developed and fairly well-nourished boy of 11 years, 61 inches in height, and 77 pounds in weight (should weigh 95 pounds). The average for this age is 53 to 56 inches and 70 to 77 pounds. The significant findings were as follows: The skin was uniformly dark. The boy appeared listless, answering questions in monosyllables with the voice of an adult male. Very slight bilateral exophthalmos and a suggestion of lid lag were noted. General muscle power was good and reflexes were normal. There was a moderate growth of pubic hair of feminine distribution, and the penis and testes were large for this age. Blood pressure was 90/50.

Diagnostic procedures were difficult to correlate and gave no early clews as to the final outcome. Repeated urinalyses, erythrocyte counts, leucocyte counts, hemoglobin estimations, and differential leucocyte counts showed no deviations from normal range. Wassermann and Mantoux tests were negative. Blood calcium, phosphorus, nonprotein nitrogen, and total protein were similarly within normal limits. However, on one occasion uric acid was 9.4 and later 8.9 mg. per cent. Lumbar puncture shortly after admission yielded fluid of normal character. There was no increased pressure, cells were not increased; sugar was 34 mg. per cent, chlorides 673 mg. per cent, total protein 74 mg. per cent. There was no excess globulin, the Wassermann reaction was negative, and colloidal gold curve flat. An x-ray of the skull and sella turcica gave no clews. The visual fields and fundi were normal.

The following is a summary of detailed metabolic studies made with the assistance of Dr. Samuel Soskin:*

Pancreas and Liver.—A number of estimations of the fasting blood sugar level yielded hypoglycemic values. An intravenous dextrose tolerance test (⅛ Gm. dextrose per kilogram body weight) started with a control fasting level of 42 mg. per cent. One-half hour after sugar administration, the blood sugar level was 213 mg. per cent, and it dropped to only 115 mg. per cent at the two-hour interval. This was a markedly "diabetic" type of curve, especially in view of the route of administration of sugar. With consideration of the hypoglycemic control level of the blood sugar, the test was interpreted as indicating liver dysfunction. A 50 per cent retention of bromsulphalein observed at about the same time was consistent with the above finding. However, blood cholesterol and cholesterol esters were repeatedly found to be within the normal range, and, at a later date, both the dextrose tolerance curve and the bromsulphalein excretion approached normal figures. It was concluded that the isolated, inconstant evidences of liver dysfunction indicated that the hepatic effects were probably not primary. The possibility was therefore

*Director of Metabolic and Endocrine Research, Michael Reese Hospital.

investigated that they might be secondary to inanition or to thyroid, adrenal cortex, or to anterior pituitary dysfunction.

Thyroid.—The observations relevant to the thyroid gland were contradictory and inconclusive. There was some exophthalmos, but the pulse rate ranged around 70 per minute, and there were no clinical signs and symptoms of hyperthyroidism. On the other hand, two basal metabolism rate determinations gave values of −22 per cent and −34 per cent, respectively. However, radiologic examination of the centers of ossification revealed that the patient's bone age was consistent with his chronologic age.

Adrenal Cortex.—The presence of weakness, vomiting, pigmentation, low basal metabolic rate, and low fasting blood sugar, with evidence of liver deficiency, suggested Addison's disease. However, a negative tuberculin reaction indicated the absence of the most common etiologic agent for this syndrome. Furthermore, the blood sodium was 561 mg. per cent, potassium 136 mg. per cent and the nonprotein nitrogen 33 mg. per cent. Urinary chloride excretion was repeatedly found to be normal. The poor clinical state of the patient precluded a provocative test with a high potassium diet.

Anterior Pituitary.—The extreme anorexia, weakness, hypotension, low fasting blood sugar level, and evidence of liver deficiency were consistent with pituitary cachexia. However, a radiologic examination of the sella turcica disclosed a normal appearance, and a therapeutic test made with an anterior pituitary preparation* resulted in no therapeutic benefit.

The above metabolic and endocrine studies as a whole were interpreted as indicating the presence of a hepatic disturbance related to dysfunction of one or more of the endocrine glands, but not permitting the diagnosis of a primary dysfunction in any of them.

Simultaneously neurologic and psychiatric consultations were requested. No new neurologic findings were present. However, the psychiatrist first suspected schizophrenia because an athletic, sociable, happy youngster with indefinite neurologic findings had become morose, withdrawn, and lethargic. But the history revealed that the boy's personality had been of a definitely outgoing type, affection for his relatives always finding free expression. He showed all the physical manifestations of a profound depression with no evidence that he actually felt depressed.

Course.—The clinical course was characterized by increasing apathy, anorexia, vomiting of all solid food, and progressive weight loss to 54 pounds at death on March 26, 1939. The temperature remained normal except for one rise to 103° F. about four months before death and several spikes during the last two months. The pulse rate varied from 80 to 90 per minute except for a terminal rate of 60 to 80. On January 1 the pupils failed to react to light and there seemed some paresis of conjugate upward gaze. However, these findings were inconstant. On February 2 no abnormalities were evident, but by February 15 all these deviations had become marked.

Two months before death a lumbar puncture showed xanthochromic fluid under pressure of 340 mm. of water, dropping to 190 mm. after removal of 10 c.c. of fluid, a total of twenty-seven cells, 80 per cent lymphocytes, and a total protein of 133 mg. per cent.

The optic disks showed no change until March 12 when an early atrophy, especially of the left disk, was noted. By March 23 definite elevation was present.

On March 7 because of right internal strabismus, loss of pupillary light reflex, paralysis of conjugate upward gaze, and bilateral central facial paralysis, a ventriculogram was made (Dr. A. Verbruggen), confirming the suspicion of an inoperable midbrain tumor.

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*Phyone, Wilson and Co., which we had previously found to be effective in a proved case of pituitary cachexia.

The first psychiatric examination on Jan. 12, 1939, found this child apathetic and speaking in a low voice. Soon he became more spontaneous and even sat up in bed, which he had refused to do formerly. He seemed extremely dependent upon the nurses, asking them to help him with simple tasks which he was quite able to perform. His urgent problem was his inability to eat. Despite his appreciation of the fact that he must eat and his repeated statements that he would, he persistently refused every meal. He evidenced fear of death from this cause and also showed anxiety for the distress that this was causing his mother and sister. But he showed good intelligence, excellent orientation in all fields, and good contact with his environment.

Subsequent examination continued to show the picture of a state of depression and of psychomotor retardation which were no different from the findings in purely functional states. He would lie for hours in bed, seemingly asleep, yet aware of what was going on, showing extreme passivity and lack of reaction to his environment. As late as Feb. 9, 1939, although he was very lethargic and had thick saliva covering his gums, when asked how he felt, the boy merely shrugged his shoulders but did not state that he was "blue" or discouraged. There was definite anxiety, however, about his death, with a peculiar fantastical acceptance of his future. These findings were present in a setting of encouragement and stimulation and the boy was unaware of his poor prognosis. He still worried because he could not eat and displayed a marked repugnance for the nasal catheter.

Despite the fact that the tumor, as will be shown subsequently, was extensive with marked pressure on the ventricles, there was no evidence of confusion or involvement of intellect. On February 15, the patient first showed evidence of toxic involvement of high cortical functions by distorting his environment with a good deal of fantasy. Showing a valentine to one of the doctors, he stated that it was a birthday card from his sister. He did not know the date but hazarded March 21. He complained that there was a snake in his bed, and again that he must chew his uncle's cigar before eating. Emotionally, he showed the marked apathy, clumsiness, and all the outward manifestations of a profound depression. It seemed that the patient was dealing with the reality of the situation first by depression, and second by an attempt to change reality with a fantasy of recovery. This is in contrast to the fantasies of the true depression, which are usually of a self-destructive nature. After this time the patient's symptoms progressed with increasing confusion and stupor, and finally death.

*Autopsy Findings.**—The body was that of a markedly emaciated but well-developed boy of the stated age, measuring 70 inches (158 cm.) in length and weighing 53 pounds (24 kg.). Axillary, mental, and pectoral hair was absent, but pubic hair was of moderate amount, soft in texture, and of feminine distribution. The external genitals showed no abnormalities, both testes having descended. The body cavities and thoracic and abdominal viscera showed no noteworthy changes.

The scalp stripped readily, and the calvarium was easily removed; the dura and meninges were of usual appearance and the vessels at the base were in usual arrangement. The brain itself appeared swollen with flattened gyri and narrowed sulci. The hypophysis showed no gross involvement.

At the base of the brain, behind the optic chiasm, replacing the substance of the base of the third ventricle, was a firm, ovoid mass, measuring 1.5 by 2.0 cm. in greatest diameters, sharply demarcated from the midportions of the temporal lobes, which caused an indentation on the posterior portion of the optic chiasm and on the anterior border of the pons (Fig. 1). The third nerves passed over this

*Under the direction of Dr. Otto Saphir, Pathologist, Michael Reese Hospital.

mass. On midsagittal section of the brain this mass was transected, and it consisted of friable, grayish-white tissue with a small central area of translucent, gelatinous tissue. This tumor compressed the right basis pontis, and occluded and pushed the Sylvian aqueduct to the left. The tegmentum was entirely replaced by similar tissue. The pineal recess was identified, but no gross vestige of pineal body was found. The quadrigeminal plate was markedly thinned, and the tumor mass had invaded the third ventricle, which in the posterior part was dilated and pushed posteriorly and upward. This tumor had almost completely destroyed the corpus callosum and had extended into the widely dilated lateral ventricle from the region of the tegmentum. Further sagittal sections showed in the anterior horn of the left lateral ventricle a round nodule, 1.5 cm. in diameter, extensions of which invaded the white matter through the lateral wall of the anterior horn. The medial wall of the ventricle posterior to this was studded with tumor nodules. The left posterior horn was dilated and pushed backward, and the temporal horn was likewise dilated. On the right the entire lateral ventricle was similarly dilated. In the anterior horn was a large tumor, measuring 5 by 4 cm. in greatest diameters, which had extended through the ventricular wall and invaded the frontal lobe to within 1 cm. of the surface of the frontal pole. This tumor pushed the basal ganglia backward. A smaller nodule, 2.5 by 2.0 cm., had invaded the lateral wall of the posterior horn.

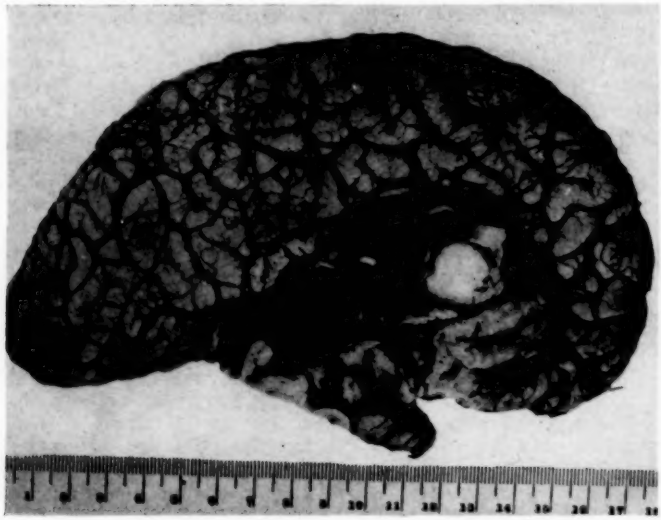

Fig. 1.—Medial aspect of left half of brain to show the involvement of the base, corpus callosum, tegmentum, and the ventricles.

Histologic Examination.—The thyroid, parathyroid, and suprarenal glands, pancreas and hypophysis showed no change. Tissue from the thymic region showed a few small collections of lymphocytes with a very occasional Hassall corpuscle. The thoracic and abdominal viscera failed to show microscopic changes.

Tumor tissue, including that from the pineal region, was sectioned from frozen and from paraffin blocks and stained with hematoxylin and eosin, toluidine blue, by the van Gieson method for connective tissue, Cajal's method for astrocytes, Stern's and Holzer's methods for glia, and by Bielschowsky's and Davenport's methods for nerve fibrils.

The tumor was composed of dense stroma in which were set the formed elements described below, the bulk of the stroma far outweighing that of the latter elements. Variously sized vessels were numerous and these were accompanied by strands of connective tissue. The cells forming this stroma showed no relationship to blood vessels, but extended in irregular, dense strands and whorls or formed loose areas between these (Fig. 2). In the loose areas were many large and smaller vacuolated areas in and about which were numerous microglia. The predominant cell of the tissue was spindle-shaped, with cytoplasmic strands forming a delicate, fibrillar groundwork. In addition to these bipolar spongioblasts, unipolar spongioblasts were fairly numerous (Fig. 3). Protoplasmic masses containing four or five closely set nuclei, similar to those of the spongioblasts, were frequent. Occasionally a rosette was identified, primitive spongioblasts surrounding a central lumen. Mitoses were numerous. Occasional stellate cells with several processes were seen and identified as astroblasts. Scattered groups of mature protoplasmic astrocytes were also noted. Besides these cells of the neuroglia series, infrequent groups of round cells with clear nuclei were distributed throughout the tissue, some cells differentiated to show cytoplasmic processes which stained as neurofibrils. These cells were identified as neuroblasts. Thus the stroma of this

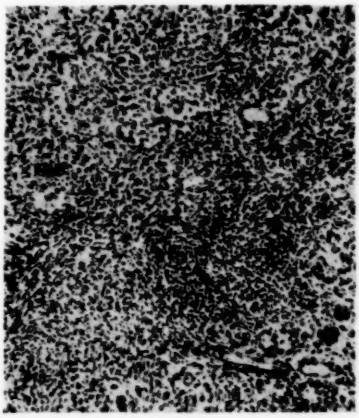

Fig. 2.

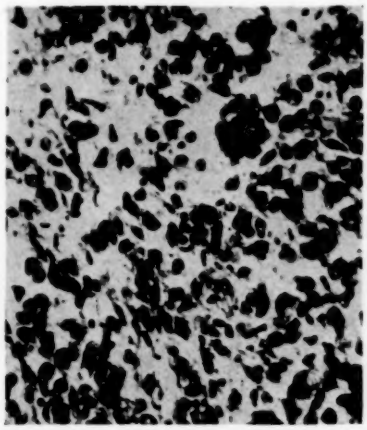

Fig. 3.

Fig. 2.—General appearance of the tumor. (Iron hematoxylin eosin, ×56.)

Fig. 3.—Tumor stroma, showing bipolar and unipolar spongioblasts and multinucleated giant cells. (Iron hematoxylin eosin, ×210.)

tumor displayed its primitive origin, developing in one direction to form bipolar and unipolar spongioblasts, and further to the stages of ependymal spongioblasts on one hand and to astroblasts and astrocytes on the other. In the other direction, cells of the neuroblast series were differentiated. Therefore, this abundant groundwork corresponded to a gliomatous tumor. The presence of both neuroblasts and spongioblasts invited the diagnosis of medulloblastoma. But the insignificance of the neural elements, as well as the striking preponderance of spongioblasts, showing numerous mitoses, with the presence of tumor giant cells and the tendency to form astroblasts and astrocytes as well as true ependymal rosettes, gave this stroma the characteristics of a spongioblastoma multiforme.

However, in this stroma nests of various types of unrelated cells occurred. Scattered throughout were small, simple, tubular glands, round or flattened, lined by a single layer of columnar, cuboidal, or flattened cells. These glands were sug-

gestive of those of the gastrointestinal tract, but ependyma could not be excluded. Elsewhere were small to large islands of compact tissue of mesenchymal origin (van Gieson), composed of oval or polygonal cells having prominent cell boundaries with homogeneous, eosinophilic material separating the cells to form an interlocking pattern. This tissue was identified as immature cartilage. Partially encircled by such tissue was a tubular structure lined by a layer of high columnar, ciliated cells with basally placed nuclei and finely granular, eosinophilic cytoplasm (Fig. 4). This was identified as epithelium of the respiratory tract (Fig. 5).

Fig. 4.

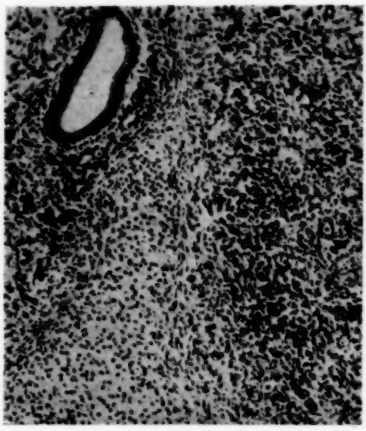

Fig. 5.

Fig. 4.—Endodermal glands. (Iron hematoxylin eosin, ×48.)
Fig. 5.—Cartilage and bronchial lining. (Iron hematoxylin eosin, ×60.)

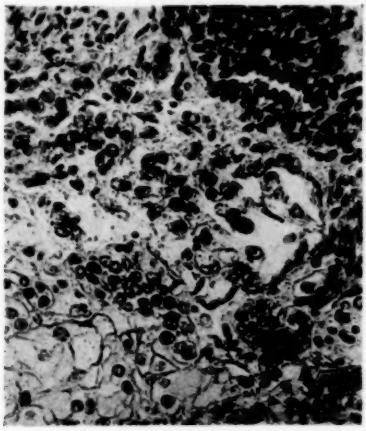

Fig. 6.—Squamous epithelium and ectodermal glands. (Van Gieson stain, ×160.)

Elsewhere were dense groups of acinar structures, simple to branching glands with central lumens, formed of pyramidal cells with basal nuclei. Scattered irregularly and sometimes in close relation to the latter glandular groups were small nests of large cells in mosaic pattern with abundant eosinophilic cytoplasm. These nests

were evident as squamous epithelium, the glands described above being of the sweat or sebaceous type (Fig. 6). Besides the above described tumor giant cells of the stroma, occasional nests of protoplasmic masses with widely spaced, oval, vesicular nuclei were present, some surrounded by a connective tissue condensation. These formations resembled chorionic giant cells, the outer syncytial layer of the villi being represented.

Sections from the region of the pineal showed the ependymal lining of the pineal recess surrounded by tumor tissue identical with that described above. However, several groups of small round cells (immature pineal cells), as well as a few corpora arenacea, were found in this region.

In summary, then, this tumor was a teratoma, its varying types of primitive tissue representing three germinal layers. Ectoderm contributed squamous epithelium, ectodermal glands, primitive cells of the neuroblast and spongioblast series, and perhaps chorionic tissue. Mesoderm contributed cartilage and connective tissue. Endoderm formed ciliated columnar epithelium of the respiratory tract and perhaps other glandular structures. The pineal origin of the tumor was evidenced by the gross replacement of the pineal body and by the microscopic identification of the pineal tissue within the tumor mass. The presence of much primitive neuroglia accounts for the tumor's invasive property and for its spread in the ventricular system. The preponderance of this tissue necessitates the additional diagnosis of a spongioblastoma multiforme, this glioma forming one element in a teratoma of the pineal body.

COMMENT

This case presents several aspects of unusual interest. It is the eighteenth reported teratoma of the pineal body. One part of the teratoma comprised a spongioblastoma multiforme which invaded widely, infiltrating the hypothalamus. The early diagnosis offered difficulty as a vague history and absence of signs suggested either encephalitis or schizophrenia. It was not until late that positive neurologic signs indicated the true condition. This case is of further significance in view of current neurologic theories (Grinker) which postulate the basal ganglia and hypothalamus as the seat of emotions. Some authors, notably Bailey, Buchanan and Bucy, report uncontrollable temper tantrums in patients with tumors of similar location. Our patient had all the outward manifestations of depression without being aware of such an emotion. Thus, he was not actually depressed. Actual emotions in modern man have a rich ideational content. Therefore, we believe that we offer an added shred of evidence that the region of the third ventricle and hypothalamus may be concerned with the expression of emotion, and not with the actual emotion itself.

SUMMARY

An account is presented of a child with an intracranial tumor which at autopsy proved a true teratoma of the pineal body. A spongioblastoma multiforme, a unilateral development within this tumor, invaded surrounding structures and spread widely throughout the brain. The child showed pubertas praecox, initial symptoms of pituitary

cachexia, and finally signs characteristic of involvement of the quadrigeminate plate and the hypothalamus. The emotional changes in the child and their significance are discussed.

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BRONCHIOGENIC CARCINOMA OF SEVEN YEARS' DURATION IN AN 11-YEAR-OLD BOY

MILTON G. WASCH, M.D., MAX LEDERER, M.D., AND
BERNARD S. EPSTEIN, M.D.
BROOKLYN, N. Y.

IN 1935 two of us (M. G. W. and B. S. E.) reported a series of cases of bronchiogenic carcinoma in which was included a boy in whom the condition had been diagnosed at the age of 11 years.[1] A biopsy taken from his right upper bronchus in 1932 had been diagnosed as adenocarcinoma. He remained under observation from 1932 to 1939, meanwhile receiving considerable radiation therapy. He died in August, 1939, at the age of 18 years. The clinical history and pathologic findings are believed of sufficient interest to warrant reporting this case.

Bronchiogenic carcinoma is known to occur during early adult life. Matz,[2] who gathered 1,814 cases from the literature, found five patients below the age of 20 years, the youngest being 13. Hochberg and Lederer[3] did not find a patient younger than 21 years in their series of sixty cases. The youngest patient in the seventy-seven cases reported by Vinson, Moersch, and Kirklin[4] was 29 years old. Arkin and Wagner[5] reported three of 135 patients between 21 and 30 years of age. Atkin[6] reported a patient 21 years old in a series of ninety-three cases, and Funk[7] noted that the youngest patient in his series of sixty-one cases was 24 years old. Cardelle and his associates[8] found one patient 11 years old in a series of 10,000 autopsies at the Municipal Hospital for Children in Havana.

Since neoplasm enters into the differential diagnosis of many pathologic states, even in the younger age groups, the question of age incidence is of more than academic interest. The interest in this case is threefold. First, he survived seven years; second, he responded surprisingly well to radiation therapy; and last, he developed an eosinophilic adenoma of the pituitary gland while under observation.

M. L., male, aged 11 years, was first seen during February, 1932. He had fever, pain in the right lower chest, and an unproductive cough for several weeks. After the fever had subsided, the pain in his chest and the cough persisted. Examination in March, 1932, disclosed suppression of breath sounds on the right upper side of his chest. A radiogram taken Feb. 20, 1932, revealed an area of opacity the size of a walnut in the right superior mediastinum in juxtaposition to the spine (Figs. 1*A* and 1*B*).

Bronchoscopic examination during June, 1932, revealed occlusion of the right primary bronchus by a mass about 2 cm. below the carina. Microscopic examination of a biopsy revealed papillary adenocarcinoma. At that time, aside from a slight cough, the patient was symptom-free.

From the Departments of Radiology and Pathology, The Jewish Hospital.

Deep x-ray therapy was started during June, 1932. Four fields, axillary, supraclavicular, and anterior and posterior upper thoracic, received a total of 1,100 roentgen units per field between June 14 and July 5, 1932. The lesion did not regress.

Fig. 1A.—Radiogram taken March 29, 1932, showing circumscribed area of opacity in the right upper lobe mesially, secondary to carcinoma of the right upper bronchus. The patient was 11 years old at this time.

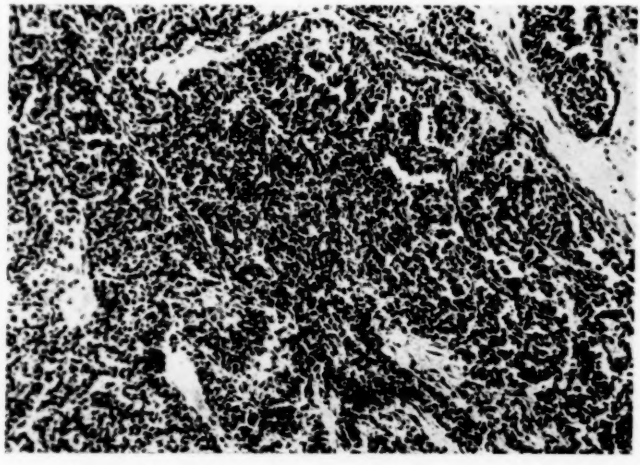

Fig. 1B.—Biopsy specimen taken March, 1932, showing low cuboidal cells arranged in nests of crude glandlike structures indicative of malignancy. (×90.)

Between September 24 and November 22, 1932, an additional 1,600 roentgen units were given to the supraclavicular and anterior and posterior superior thoracic fields.

Cough, weakness, and chest pain persisted. A radiogram of his chest on Nov. 23, 1932, revealed an increase in the opacity of the right lung suggestive of an exudative process. On Dec. 5, 1932, there was complete opacity of the entire right lung field, with shifting of the mediastinum toward the affected side, indicative of pulmonary collapse.

During January, 1933, a 100 mg. radium pack was applied to the right upper chest anteriorly and posteriorly and to the right axilla for a total of 10,800 mg. hr. Following this, the right lung again became aerated. The opacity in the right upper chest was greater, however, than that prior to the atelectatic episode, and the diaphragm became elevated, as demonstrated by the radiogram taken April 24, 1933.

He felt relatively well for the next eight months. His weight increased from 75 to 115 pounds, and he was able to attend school and participate in athletic activities. A chest radiogram taken Sept. 18, 1933, corresponded to the study of the preceding April.

During January, 1934, pain in the right chest and slight hemoptysis occurred. Physical examination showed a flat percussion note over the right chest, with limitation of motion during forced respiration. A teleoroentgenogram made Feb. 7, 1934, revealed increasing density, progressive elevation of the right diaphragm, and shift of the mediastinum to the right. He remained quite well until November, 1934, except for occasional cough and bloodstreaked sputum. At this time he was given further radium therapy, receiving 7,200 mg. hr. over the original three fields.

Fig. 2.—Radiogram of chest four years after original examination. The mediastinal contents are displaced toward the affected right side; pronounced inequality of the lung fields, due to right pulmonary collapse, is present, and the diaphragmatic shadow no longer can be identified.

His condition was satisfactory until March, 1935. He was then readmitted because of recurrence of cough and bloodstreaked sputum. A total of 7,200 mg. hr. of radium therapy again was administered.

Following the last radium treatment, the patient felt well and gained considerably in weight and stature until 1939. During 1935, it was noted that his rate of

growth was inordinate. Coincident with the rapid development, a marked asymmetry of his chest became apparent. The right upper thorax appeared to sink, while the left gradually assumed a barrel-shaped configuration as a result of compensatory emphysema. His left shoulder dropped, and an upper dorsal scoliosis appeared. Both hands and feet became unusually large; his face became full and his features coarse. Radiographic examination of his skull during November, 1934, and June, 1939, showed a normal sella turcica. Radiographic examination of his chest during May, 1936, revealed considerable shrinkage of the right lung and emphysema of the left lung. The mediastinum was shifted toward the right, and the right diaphragm could not be identified. (Fig. 2.)

During June, 1939, hemoptysis, increasing dyspnea on exertion, tachycardia, and progressive weakness developed. He was readmitted to the Hospital on July 5, 1939. He weighed 190 pounds and was 6 feet 4 inches tall. Radiographic examination of his chest showed no apparent change from the study of 1936. Swelling of the abdomen, followed by generalized anasarca, extreme weakness, dyspnea, and orthopnea, soon followed. No murmurs were heard over his precordium. The liver and spleen were not palpable. Routine laboratory examinations throughout the entire course of the disease were not contributory. He died Aug. 18, 1939, in cardiac failure.

The condensed autopsy protocol is as follows: "The body is that of a male, 190 cm. long, weighing 100 kg. There is pronounced pitting edema over the ankles, scrotum, and sacrum. Many narrow pale striae are seen over the abdomen. The lower jaw is prominent, the teeth widely separated, and the features coarse. The hands and feet are disproportionately large, the former being spadelike with thick fingers. The thorax is asymmetrical; the left is bulging and barrel-shaped in contrast with the right half, which is small and sunken. The upper anterior and supraclavicular areas of the right thorax are tanned. Scoliosis of the upper thoracic spine with convexity to the left is present. The abdomen is protuberant. The right testis can be palpated in the inguinal region; the left is in its normal position.

"The peritoneal cavity contains about 800 ml. of clear yellow fluid. The right pleural cavity is completely obliterated by firm adhesions. About 300 ml. of clear yellow fluid are present in the left pleural cavity. The pericardial cavity is completely obliterated.

"The external surface of the left lung is mottled gray and purple in color. In the lower lobe there is a small, sharply demarcated, spherical mass measuring 3.5 by 3 cm. The remainder of the lung is normal.

"The right lung is represented by a stump of firm, slightly nodular, densely hyalinized tissue containing areas of calcification. The entire lung measures 5.2 by 4 by 4 cm. after removal. On section, a few remnants of gray lung tissue separated by dense white strands can be recognized. The right main bronchus leads into this mass and can be probed for a short distance. Adjacent to the stump there are several firm lymph nodes which are infiltrated with neoplastic tissue.

"The heart valves are normal. The right and left ventricular walls measure 2 and 4 cm., respectively. Numerous metastatic nodules project into both ventricles. There are also deposits in the interventricular septum. On section, these consist of firm, well-circumscribed, spherical nodules varying from 0.5 to 4 cm. in diameter. The endocardium is smooth and glistening throughout. The coronary arteries and great vessels appear normal (Figs. 3*A* and 3*B*).

"The liver is enlarged, weighing 3630 Gm. No metastatic lesions are present. On section, the cut surfaces present the picture of acute congestive changes with areas of necrosis in the peripheral portion of the right lobe and, to a lesser degree, in the periphery of the left lobe.

"A well-circumscribed, firm, gray, metastatic nodule measuring 0.3 cm. in diameter is seen on the surface of the left kidney, and three similar nodules

Fig. 3*A*.—Stump of the right lung (*A*), emphysematous left lung (*B*), and metastatic foci in the wall of the left ventricle (*C*).

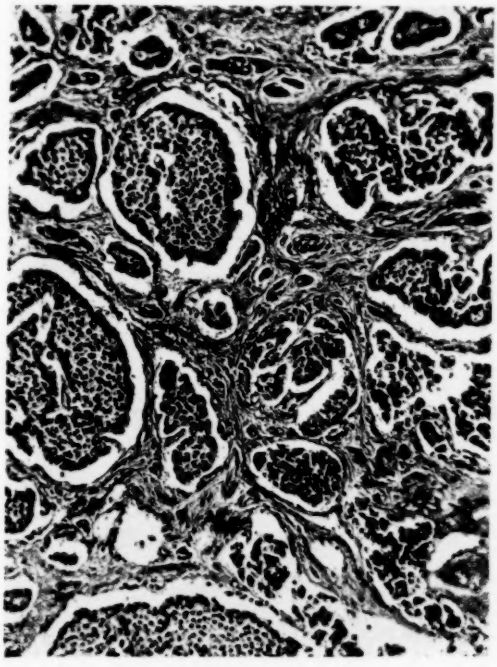

Fig. 3*B*.—Nests of metastatic tumor cells in myocardium. (×400.)

are seen on the surface of the right kidney. The adrenals and the pancreas present no abnormalities.

"The dura mater has two pedunculated, firm, irregular, lobulated nodules attached to it, mensuring 1 cm. in diameter each. The cerebral hemispheres are normal.

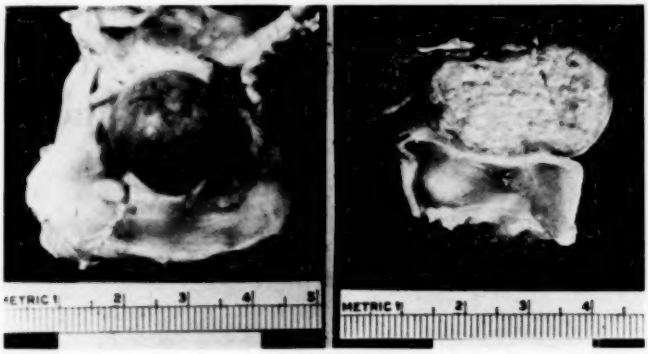

Fig. 4*A*. Fig. 4*B*.

Fig. 4*A*.—Pituitary gland in situ, showing adenoma of anterior lobe.
Fig. 4*B*.—Sagittal section of pituitary gland resting on floor of sella turcica.

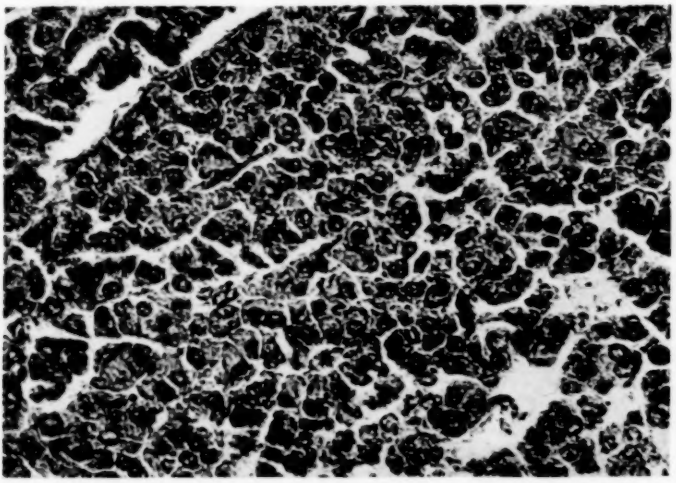

Fig. 4*C*.—Section from adenoma of anterior lobe of pituitary gland showing preponderance of eosinophilic cells. (×800.)

"Projecting from the sella turcica at the site of the anterior portion of the pituitary gland is a rounded, well-encapsulated body about 2 cm. in diameter, apparently springing from the anterior lobe of the hypophysis. The sella turcica is somewhat expanded, but no erosion is noted. The clinoid processes are intact (Figs. 4*A*, 4*B* and 4*C*).

"Microscopic examination of sections taken from the nodules in the myocardium reveals cells characterized by pink-staining cytoplasm and large oval vesicular nuclei

and prominent nucleoli. The nuclei vary considerably in size and staining reaction and show an occasional mitotic figure. In places these cell groups appear to form lumina and imitate glandular structures. They bear a striking resemblance to

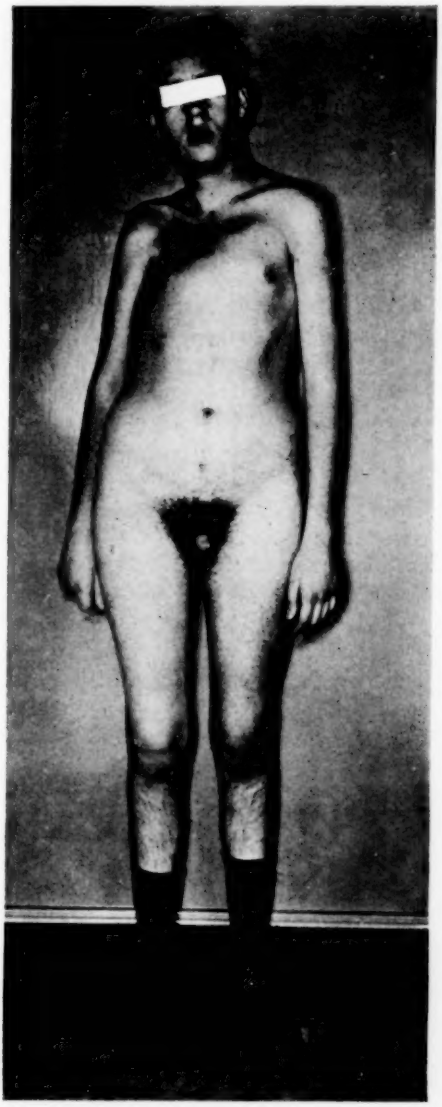

Fig. 5.—The patient at the age of 18 years, seven years after the established presence of a bronchiogenic carcinoma. He was 6 feet 4 inches tall. Note the collapsed right upper chest, coarse features, and underdevelopment of the genitals.

the cellular structure of the biopsy removed from the right main bronchus early in the patient's illness.

"Sections taken from the right lung stump show deeply pink-staining hyalinized connective tissue, interspersed in which are nests and cords of tumor cells. The cellular structures of the nodules in the left lung likewise resemble the tumor cells seen in the original biopsy. The microscopic structure of one of the lymph nodes taken from the region of the right main bronchus shows complete replacement of the lymphoid substance by nests of tumor cells in which the lumina are clearly recognizable. The nodules in the kidney and meninges present similar histologic characteristics.

"In a midsagittal section through the pituitary gland are cords and nests of cells resembling those normally found in the anterior lobe. The distribution is quite abnormal in that the greatest number are of the eosinophilic variety, the chromophile and basophile cells being very scant."

SUMMARY AND COMMENT

The history and autopsy findings of a patient with a proved carcinoma of the bronchus for seven years are reported. He died at the age of 18 with visceral metastases. The immediate cause of death was accretio cordis. The patient had been under observation since the age of 11 years, when the diagnosis had been made and confirmed by biopsy. The histologic structure of the original biopsy and the metastatic lesions in the heart and viscera were similar. There was a coincidental adenoma of the pituitary gland, associated with gigantism (Fig. 5).

The radiation treatment consisted of 9,200 roentgen units of deep x-ray therapy given between June and November, 1932, and 25,200 mg. hr. of radium therapy administered in three séances between January, 1933, and March, 1935. No radiation therapy was given during the last four and one-half years of the patient's life. It is our impression that the radiotherapeutic response in this case was enhanced by the use of radium. Other cases treated by us solely with deep x-ray therapy did not respond as favorably.

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A HEALTH PROGRAM FOR THE STAFF OF A CHILDREN'S HOSPITAL

HENRY H. WORK, JR., M.D.
EAST PROVIDENCE, R. I.

MAINTENANCE of the physical health and mental well-being of the staff of a hospital, while not universally accepted as the duty of an institution, is certainly in accord with the principles of good medicine. In addition, it is an economically sound practice and one that pays dividends both in increased efficiency of the workers and in the promulgation of public health measures.

In spite of the fact that many industrial concerns have set up all-inclusive plans for the care of the health of their employees, a review of the medical literature suggests that hospitals, in their effort to serve the patient first, have not expended a corresponding effort on the care of those whose duty it is to administer this service. This impression is further confirmed by a survey conducted by the Academy of Pediatrics covering the entire personnel of children's hospitals.[1] More has been written about the need for extra attention to the health of nurses, and from the number of articles on this subject it would appear that most hospitals make definite attempts to care for these important members of the staff. This may be due, perhaps, to better organization among the nurses, and it may be that the paucity of material dealing with the care of the medical, administrative, maintenance, and dietary staffs can be explained by the fact that these groups have demanded less care.

It may be, however, that, although efficient plans are in operation, they have not been described, and it is for this reason that we are here presenting the measures used in the management of the health of employees at the Emma Pendleton Bradley Home. This fifty-bed hospital for the care of children with neuropsychiatric disorders has more than the usual number of employees. Because of this the attention paid to their health is an important factor in the effective operation of the hospital.

ROUTINE MEASURES

The plan to be presented has been evolved over a period of years and incorporates certain routine measures which apply to all members of the staff. Also, it involves certain steps which are taken not only for the prevention of illness but also for the treatment of such sickness as may arise.

At the time that each individual joins the staff of the hospital, he is interviewed by the medical director as well as by the head of the department in which he is to be employed. In this manner his personality may

From the Emma Pendleton Bradley Home, East Providence, R. I.

be assessed and an estimate made of his potential ability to adjust to his task. When good personal rapport has been initiated in this fashion, the employee feels free to bring any problems in connection with his work to the attention of the medical director. Advice in the conduct of perplexing situations is freely given to all employees.

When the new employee reports for work, he is given a thorough physical examination, and a record is made of his past medical history. For these procedures the outline suggested by the American Medical Association has been followed.[2] At the same time, in accordance with the suggestions made in recent public health campaigns, blood is taken for serologic examination, and a culture is made from swabbings of the nose and throat for the presence of diphtheria organisms. An x-ray examination of the chest (including fluoroscopy) is required of each person. In order to emphasize the personal value of this procedure, the employees are assessed a portion of the total cost of the plates: those earning more than twenty-one dollars weekly contribute two dollars toward the payment, while those earning less pay one dollar. All abnormalities discovered by any of these procedures are called to the attention of the individual, and he is encouraged to consult the medical director concerning the results of the studies. (It should be mentioned that none of the patients are suffering from tuberculosis.) For further protection of both individual and community health all of these steps are repeated once each year.

Certain other routine measures which apply to the relationship between the staff and the patients are in use. Of these, the most important is the wearing of masks, which are of the filler type with three insert layers of gauze. These have been used by the staff during the past two winters with an appreciable decrease in the incidence of upper respiratory infections. This has been noted chiefly among the patients but to some extent among the staff. Masks are especially important because many of the staff do not live in the hospital, and new varieties of respiratory flora are constantly being introduced. Wearing of the masks applies to all members of the personnel who are in direct contact with the patients. This includes, in addition to the medical and nursing groups, members of any other staff, such as maintenance, who may be doing work on the wards. It has even proved possible to teach school for an entire day while wearing a mask. Parents and other visitors are required to wear them throughout their stay on the ward. Masks are discarded when outdoors, even though the adults may be in some contact with the patients.

MANAGEMENT OF SICKNESS

Other routine procedures are used in the management of epidemic disease. For the more contagious diseases a strict quarantine is imposed, and all patients or adults presenting suspicious signs are isolated. Depending upon the severity of the epidemic and in accordance

with the restrictions of the specific disease, members of the staff are sent either to their own homes or to a contagious disease hospital.

Special provisions are made for the general care of sickness among the employees. A staff clinic is held by the medical director twice a day and all adults with any complaints, however slight, are expected to report to the doctor at these times. A member of the medical staff is on call at all times to attend to emergencies arising among the employees as well as those among the patients.

Minor illnesses are dealt with at the time of the clinic, and the necessary treatment is given either by the physician or by a member of the nursing staff designated as the "infirmary nurse." No infirmary is maintained, however, and all bed care for employees who live in the hospital is provided in their rooms. This is possible only in instances of minor illnesses such as would ordinarily require only home care. All cases needing hospitalization are sent out, the expense of this being borne by the employee. (In this connection it should be mentioned that all members of the staff are encouraged to subscribe to the "Blue Cross" hospitalization plan,* and 75 per cent of the employees have taken advantage of this opportunity.)

When an employee is confined to his room, he is supplied with fundamental nursing care and meals. The medical director treats these patients with the assistance of outside consultants when necessary. The patient is not allowed to have visitors, a measure intended primarily to decrease the spread of infectious diseases, particularly those of the upper respiratory tract. A secondary but by no means unimportant aspect of the measure is the psychological effect both in giving the patient complete rest while he is ill and in speeding his convalescence when he has recovered. The elimination of the infirmary as an economic measure is another factor which has brought about a reduction of the number of days lost through illness.

When members of the staff who live outside the hospital are sent off duty, it is expected that they will place themselves under the care of their personal physicians. The hospital maintains no formal contact with these employees, but they must be re-examined by the hospital physician before returning to their work.

The hospital carries compensation insurance which provides care for all injuries sustained in the line of duty. Employees sustaining accidental injury are seen at once by the medical director, and treatment is ordered, or they are referred directly to the care of one of the physicians on the consulting staff. In the latter instance they remain his patients throughout the illness. In addition, the hospital annually allows one week of sick leave with pay to all employees. Sick leave may extend beyond this initial week, but no further compensation is given. This

*The local group hospitalization insurance plan is referred to as the "Blue Cross" plan.

leave may involve nursing care, or, as in the case of certain minor injuries, merely maintenance.

During the years that this plan has been used in the hospital the number of days lost through illness has constantly decreased. In the last year the average was less than three days' sick leave per person. These results attest both the efficacy of the plan and its economic value.

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Critical Review

PLAY INVESTIGATION AND PLAY TREATMENT OF CHILDREN'S BEHAVIOR DISORDERS

LEO KANNER, M.D.
BALTIMORE, MD.

INTRODUCTION

ALL scientific curiosity keeps in wholesome flux by regenerating itself constantly or in spurts through the discovery of hitherto unknown facts, the reshuffling of facts already known, the establishment of ever more relationships and pertinences, and the introduction of modified or novel methods of inquiry.

The entire field of child psychiatry owes its relatively recent origin to a fruitful departure from an outlook which had considered stars, rocks, fossils, and plants, but not live human beings, as worthy objects of organized research. Man, as far as science was concerned, figured mainly as a container of more or less dissociated items, some of which were selected for special reference by medicine, others by anthropology, ethnology, sociology, psychology, pedagogy, and jurisprudence. Familiarity with organs, symptoms, syndromes, diseases, tribal customs, statistics, laws, and scholastic curricula did not add up to familiarity with any one individual's life as it is lived. It is almost inconceivable that all those pieces were not picked up until a generation or two ago and recognized as intrinsic components of persons as integrated units interacting with other such units. The admission of man or "the person as a whole" (so a current slogan has dubbed him) as a legitimate object for investigation is doubtless one of the greatest and most breath-taking advances of contemporary science.

New goals call for new ways to reach them. In the attempts to find ways to study man, there has been an abundance of formulations, methods, approaches, and techniques, sometimes evolving from each other, sometimes supplementing or broadening each other, and at times clashing with each other. An unprecedented challenge lay in the fact that here, for the first time, the observer was confronted with "material" far more complex than that of any other science, that every sort of inquiry immediately created a personal relationship between examiner and examined, that a considerable and, in fact, endless variety of people, issues, and circumstances defied generalizations and classifications so helpful in the other sciences. Some performances of man seemed to be, at least within limits, accessible to the accustomed type of study and recording. But man, unlike any other object of research, is of the same stuff as the researcher himself; he acts, thinks, feels, speaks, can express his feelings and thoughts or withhold expression, can reveal, conceal, or sham his emotions and motives, of which often enough he is not himself clearly and fully aware. Language comes to take on an indispensable part both as "stimulus" and "reaction." In dealing psychiatrically even with adults whose language

is adequately developed, it was found that often mere conversational use of this tool did not quite suffice. Means were devised to "get at" the patient, to gain greater intimacy and precision through procedures such as hypnotism, word association tests, ink blot (Rorschach) tests, the study of visceral and psychogalvanic concomitants. One group has gone so far as to build hypothetically into man an elaborate meshwork of personified forces and mechanisms and to "interpret" behavior by attributing a person's utterances, elicited with certain rituals, to the influences of those postulated forces and mechanisms.

The language of children, developing gradually, limited in vocabulary, incapable of abstractions, unskilled in relating experiences, is still less adequate in allowing one to "get at" the little patients, their attitudes, attachments, aversions, anxieties, expectations, and disappointments. Child psychiatry, in its beginnings, used language primarily for psychometric testing and whatever could be gained through question-and-answer interviews. For the rest, the direction of inquiry went toward an exploration of childhood disorders as compared with adult disorders, organically determined anomalies of behavior and personality, and the results of environmental influences and impacts. These studies yielded immensely valuable information and frequently were all that was needed. Yet, in a way, the children were "left out in the cold." Therapy was arranged largely *for* the children and only to a limited extent *with* the children. Some investigators began to look around for ways in which the patients themselves might have an opportunity to express themselves revealingly. Would it be possible to learn how a child himself feels, what it is that disturbs him? Would not our knowledge of situational stresses be happily supplemented if we knew what those stresses really mean to the child who is exposed to them?

No one could have given a better answer to these questions than the children themselves. A glimpse at the nursery and at groups in action not arranged for them by adults offers at once an invitation to make use of that essential part of child life which we call *play*. A child, when playing, draws on his own spontaneity, initiative, and imaginativeness, creates artificial situations so much without artifice that they become artistically natural, weaves his life experiences and emotional attitudes playfully and yet seriously into performances seemingly remote from "reality."

STUDIES AND EXPLANATIONS OF CHILDREN'S PLAY

The play life of children has been investigated from various angles.[36] Game preferences of boys and girls were compared. The time consumed in play by children of various ages was recorded; the average length of time spent with one single game or toy was measured. The popularity of individual games or toys was ascertained. Relationship between play and health, play and intelligence, play and personality features was studied. Some attention, decidedly less than the issue merits, has been paid to the anomalies of play life, for instance, complaints that a child's interests are completely absorbed by play to the exclusion of everything else, that a child does not play at all, that a child does not seem to know how to handle or what to do with his toys, or that a child is unable to play normally with other children.

Many theories have been formed about the nature of children's play. The *surplus energy theory* assumed that in play a child "blows off

steam," as it were. Friedrich Schiller,[42] the German poet, spoke of play as "the aimless expenditure of exuberant energy." According to Herbert Spencer,[45] it is an expression of the energy left over after the necessities of life have been satisfied. Spencer added that the forms of play (of young animals) tend to take the forms of adult activities of the same species. This remark can be regarded as a transition to the so-called *instinct-practice theory*, introduced by Karl Groos.[21] Play, according to Groos, derives from an instinct to serve the purpose of education. Man does not play because he is young, but is made by Nature to go through a period of childhood in order that he may play and thus prepare himself for adult activities. The *recreation theory*, accredited to Moritz Lazarus,[27] held that play is the satisfaction of a physiologic need for relaxation: "After work we require rest which accomplishes recuperation. But hardly ever does mere empty, inactive rest suffice for recuperation." Patrick,[39] enlarging upon this idea, declared that at the present stage of human evolution there is greater exercise of mental powers than previously and, therefore, greater mental fatigue. Play is an escape from such fatigue by reverting to phylogenetically older, "deep-rooted race habits" which involve the relaxing use of the big muscles. The *recapitulation theory*, advocated by G. S. Hall,[23] went even more definitely back to the history of the human race for an explanation of the nature of play. The growing child was said to pass through a series of stages which recapitulate the "culture epochs" in the evolution of the race: animal, savage, nomad, agricultural, and tribal. Said Hall: "I regard play as the motor habits and spirit of the past of the race, persisting in the present, as rudimentary functions. . . . This is why the heart of youth goes out into play as into nothing else, as if in it man remembered a lost paradise."

More recent explanations have drawn on psychodynamics rather than on physiology and anthropologic inheritance. The *catharsis theory* considers play as a sort of safety valve for pent-up emotions; the child "plays out" his conflicts. The *self-expression theory* has been summed up best by Mitchell and Mason:[37] "Children find in play the medium for the satisfaction of the great majority of their motives. Indeed, to children play *is* the serious business of life." Play is the natural and most readily available outlet for a child's needs and feelings, which cannot, as in the adult, be worked out verbally, vocationally, and in many other ways not accessible to a child. "Children play," Seashore wrote,[43] "as do the rest of us, because it satisfies certain cravings and seems to be the eternally fit and natural thing to do." Much of a child's personality, disposition, mood of the moment, fantasy life, wishes, fears, love, and hatred expresses itself through play, in which there is no need to "adjust" to the presence and curiosity of potentially interfering elders. Baldwin said:[5, 6] "The child himself sets the limitations of the game, makes the rules and subjects himself to them, and then in time pierces the bubble for himself, saying, 'I will play no more.' All this is the germ of self-regulation, of the control of the impulses, of the voluntary adoption of the ideal, which becomes in later life, if so be that he cling to it, the pearl of great price." As far back as 1826, Froebel stated:[18] "Play then is the highest development in childhood, for it alone is the *free expression* of what is in the child's soul. Childhood's play is not mere sport. It is full of meaning and serious import. Cherish it and encourage it.

For to one who has insight into human nature, the trend of the whole future life of the child is revealed in his freely chosen play."

PSYCHOANALYTIC PLAY INTERPRETATION AND PLAY THERAPY

Lowrey has said recently:[35] "Most of us who have been long in the field of children's work began very early to use toys, pictures, drawings, and modellings as a means of uncovering children's wishes, fantasies, hostilities, jealousies, and transference." The first attempts to include play in any sort of psychiatric work with children were, indeed, intended to "uncover, reveal, disclose" the feelings and motives underlying difficulties of behavior. The first investigators, however, being adherents of the psychoanalytic doctrines, did not find it necessary to learn what a child's play activities meant to *him*, what *he* expressed in this fashion. Instead, they applied to their observations or fragments thereof their ready-made formulas and immediately "interpreted" those activities in terms of their own theoretical preoccupations. They studied play for what it signified, not to the playing child, but to the observing adult. Hence, the interpretations were colored strongly, if not dominated completely, by preconceived notions of what certain play activities should, rather than what they did, signify and express.

To Hug-Hellmuth[25] goes credit for the introduction of play into child analysis. She stated that, when dealing with children of 7 or 8 years of age, the analyst can often pave the way by sharing in the play activities and thus recognize several symptoms and character traits. Just how she proceeded to "recognize" is best illustrated by the example of a little boy who "took his gun and said: 'Puff! Puff!'" This was immediately interpreted as meaning that the child nurtured a death wish against his father. When the boy ran out of the room, perhaps tired of having every move that he made interpreted to him thus, this act was labeled as an "avowal (of the death wish) expressed without words, in a symbolic act."

This type of interpretation achieved veritable orgies in the analyses reported by Melanie Klein.[26] She let the children come to her for hundreds of hours and play, pelting upon them her dream-book kind of explanations of what their playful acts meant to her. A few of her dicta may serve as illustrations.

Item: "Behind every form of play activity lies a process of discharge of masturbatory fantasies, operating in the form of a continuous impulse to play."

Item: "Arithmetic and writing represented violent sadistic attacks upon her (Erna's) mother's body and her father's penis to her unconscious. They meant tearing, cutting up, or burning her mother's body, together with the children it contained, and castrating her father."

Item: "Reading, in consequence of the symbolical equation of her mother's body with books, had come to mean [to Melanie Klein, not to the child!] a violent removal of substances, children, etc., from the inside of her mother."

Item: "In his (Egon's) case, as in all analyses of boys, making a cart move along meant masturbation and coitus, making carts hit together meant coitus, and comparison of a larger cart with a smaller meant rivalry with his father or his father's penis."

Item: "I said that her (Ilse's) continual smoothing out of the folds of her dress meant both masturbation and an attempt to repair her genitals."

Item: "The unruly behavior of children while being bathed or having their hair washed is nothing but a hidden fear of being castrated or having their whole body destroyed."

Item: "A child's dislike of taking an object out of a box will not infrequently be due to the fact that doing so signifies an enactment of its fantasy of making an attack on its mother's body."

Item: "Nose-picking, in both children and adults, has turned out to represent, among other things, an anal attack on the bodies of their parents."

The citation of further examples does not seem necessary. If a child, overcome by the analyst's authoritative decrees, said nothing in response to such enlightenment, he was described as "accepting" the offered interpretation. If he expressed disapproval, he either was not ready to accept and needed more dozens of analytic hours or the very denial was a sign of "unconscious" confirmation. Besides, the fact that he came back (brought or dragged back by an adult) for the next session was proof that he was in agreement right along. It did not really matter how a child played, for whatever he did, he was told that he was unconsciously masturbating, cohabitating (preferably with a parent), evidencing an appetite for his father's penis and his mother's breasts, or tearing up his mother's body.

Anna Freud,[16] far less imbued with a sense of interpretive omniscience, used direct explanations to children much more sparingly. She depended more closely on an understanding of the entire setting in which the patient's difficulty had developed. She did not disregard the material obtained from parents concerning the child's everyday activities. The situation of the present was not forgotten over the psychoanalytic compulsion to ascribe etiological value only to a dogmatically construed past. She used play to a considerable extent as a means of getting acquainted with her patient, gaining his confidence, making herself liked by him. Only after she had gained sufficient knowledge of the child, his problems and his environment, did she offer interpretations directly to the child. These interpretations, it is true, had all the flavor of Freudian symbolism.

Psychoanalytic play therapy soon became a definite part of child analysis. Gerard,[19] Liss,[34] Lippman,[33] and Gitelson[20] are some of its more recent practitioners. There has been some departure from the unbridled behavior of Melanie Klein. Gitelson stated: "At this point it must be noted and emphasized that no interpretations of deep, unconscious mental content have been given to any of the patients." But the interpretations, that is, the translations of a child's actions and utterances into a prearranged code, go on as lustily as ever in those quarters. Sometimes real and sometimes lip service is paid to the circumstances from which the children come and to which they return. But to the analysts, the interpretations born of their own fancy are the chief "reality" that counts. A sober observer cannot help but gain the impression that in this type of play therapy there are two participating players: a seriously playing child expressing his attitudes toward

himself and the world, and a not less seriously playing adult "interpreter" injecting and projecting his own naive phallic *Weltanschauung.*

Rogerson,[41] in a recent monograph published in England, has convincingly demonstrated the needlessness and, in fact, the interference of interpretations in play work with children. He said: "There is a great need for non-interpretative play therapy, for it offers a key to the understanding of the child's mind. This process of understanding must necessarily be a gradual one: in each case there is much that will remain obscure to become unravelled gradually as further cases accumulate. . . . Interpretations and suggestions speedily reduce the experimental value of the work. The therapeutic necessity for them has been challenged in this [Rogerson's] work, and it is felt that their place in treatment should be carefully revised."

STANDARDIZED PLAY SITUATIONS

D. M. Levy,[29, 30] setting out to study problems arising from sibling rivalry in children, tried to "shape the play situations into essentially similar forms" by "utilizing the same play material and the same stimuli words." He introduced the use of the amputation doll, a metal doll which can be dismembered and restored.

The procedure is described as follows:[30] "The patient is told that we are to play a game. For the game we need a mother, a baby, and an older sister (or brother). We use the amputation doll to represent the mother, a celluloid baby doll, and a larger doll for the older sister (or brother). The examiner says, 'The mother must feed the baby.' He then points to the chest of the amputation doll and says, 'But she has no breasts. Let's make some.' The examiner makes one breast, and the child makes the other. . . . After the breasts are placed in position on the mother doll, the baby doll is put in the nursing position, the mother's arms encircling it. The child is asked to name the baby and the sister (or brother).

"The examiner then says, 'Now, this is the game. The sister comes and sees a new baby at the mother's breast. She sees it for the first time. Now what does she do? Do whatever you think.' The child is encouraged with such phrases as 'Go ahead,' 'Don't be afraid.' The experiment may be repeated several times.

"After the 'controlled' situation has been utilized in this way, the examiner may then stimulate activity in various ways. These methods of releasing the rivalry . . . consist largely in using such phrases as, 'When the sister saw the baby she thought, The nerve, at my mother's breast!' Or the child is told, 'That's really your baby brother and this doll here is you.'

"We have, then, two types of experiments. In the first, the same situation is presented to each child, who is activated largely by the situation presented, with no suggestion as to the direction of the activity. In the second, a stimulus is given for the purpose of releasing rivalry feelings."

A child, thus confronted with dolls and expected to act spontaneously or in response to the described kind of "encouragement," does one of several things. If he moved toward the dolls, this was considered a manifestation of hostility. Dropping, flipping, and slight

denting of the baby doll were regarded as mild attacks; throwing, slapping, and hitting were held to be evidences of assault; crushing, tearing apart, and biting were declared to be primitive forms of aggression. "In general, the child displays an increasing variety of forms and intensity of hostile behavior with increasing repetitions of the experiment. However, as hostility is facilitated to more primitive forms, it may favor one object over the others, although the baby doll is more frequently and increasingly attacked."

If the child did something unkind to himself or the doll representing himself, this was looked upon as self-retaliatory or self-punishing behavior.

If the child went after the examiner, this was believed to serve "to pass the blame of hostility on to him, hence to punish him instead of the subject." The child thus indulged in "projected self-accusation and punishment."

If the child remained altogether inactive or "refused to cooperate," if, instead of moving toward the group of dolls, he moved away from it, if he hit some other object in the room and not one of the dolls, then these acts were explained as "kinds of activity utilized to inhibit or prevent hostile behavior."

In other words, regardless of what the child did, his conduct was declared to be an expression of manifest, projected, or inhibited hostility and aggressiveness, or self-punishment, self-accusation, or self-retaliation for the wish to be hostile and aggressive. Since nothing that a child did was ever construed as nonhostile (even "mothering the baby" was supposed to "represent concealment of hostility"), it follows that every act of every child was "hostile" by definition. The performance was standardized to the point of interpretive stereotypy.

Louise Despert stirred up "a phase of increased destructiveness" by a standardized play method which made use of a knife "under certain circumstances." The children (twenty-two patients of the Children's Service of the New York Psychiatric Institute) were shown a sharp knife, and the physician discussed "at length the difficulties and dangers involved in handling a knife." The children were told that they were to scrape a piece of cardboard and that they were being locked in a room, so that the other children in the ward might not come in and use the knife "inadvisedly." They were left unobserved in the room for one hour. They were interviewed immediately after the daily scraping period and asked questions such as, "What can one do with a knife?" "Suppose you could do anything you wanted, what would you do?" The resulting material contains statements concerned with "cutting," "murder," "killing," "death," and "cutting bellies." The procedure is based on the belief that a child cannot improve unless he find release through aggressive expression. The same purpose was also sought by means of drawings (by the hundreds), retelling of stories, and group play or "collective fantasy." The results of the stories, drawings, and statements about the use of the knife were used for interpretations given out to the children. The main aim was to drive out the old devil aggression which was believed to inhabit the patients. A choreic girl who was given the knife to cure her of her compulsions (!) sustained several cuts. The author leans heavily on psychoanalytic concepts.

Emphasis on "aggression" coupled with "the problem of the child's love relationship with its father and mother and siblings" is placed by Bender and Woltmann[7] in their psychoanalytic interpretations of puppet plays presented at the Children's Observation Ward of the Psychiatric Division of the Bellevue Hospital. "The hero of all our puppet plays is Casper," originally a product of German folklore. The most popular story, "Casper in Africa," is here reproduced in order to give an illustration of the ensuing "interpretations":

"Casper is travelling and finds himself in a new country. He is very hungry and looks for food. He finds bananas growing on a tree, and takes one but puts it down for a minute and turns his back. A monkey comes out and snatches the banana. Casper turns about, is surprised but gets another banana and this too is taken by the monkey, unknown to Casper, in the same way. This is repeated many times. The children tell Casper that it is the monkey and advise him to get his stick. Then there is a frequently repeated play between the monkey and Casper, with the stick and the banana. First, Casper knocks the monkey down with the stick, and while he goes for the banana, the monkey comes and gets the stick and knocks Casper down. Finally, they have a wholehearted fight, and in the end Casper asks the children if he shall not let the monkey be his friend so he can help him get food. The children readily acquiesce and Casper names the monkey Charlie. Charlie wanders off, and Casper finds a treasure for his mother, a feather broom, and lays it down; an alligator comes in and swallows it. When Casper returns and finds the broom missing, he blames Charlie, although the children defend Charlie. Charlie comes in and Casper beats him. Then the alligator comes and tries to eat both of them. The children advise Casper to get his stick, and Casper and Charlie try to hit the alligator. There is again considerable repetition of the hitting and biting until the alligator is killed by Charlie. Then, while Casper is sleeping to rest from his labors, two native cannibals come on the scene and carry on some native dances and speech. When they see Casper they try to kill him and he is advised by the children to get his stick and call Charlie, and again there are frequent repetitions in which one or the other is about to win until Charlie again saves Casper from the natives."

What do the authors make of the "observation of the groups of children at the time of the play, hearing what they have to say afterward, either in groups with questionnaires, or in individual interviews with the psychiatrist or the puppeteers"? They simply get out their psychoanalytic cliché and "interpret" (mostly in wholesale). They decree that Casper "represents something of the ego ideal in the psychoanalytical term of Freud"; that the stick, a phallic symbol, represents aggressiveness and fertility; that the monkey "represents that part of the child's own personality which is defined by Freud as the id"; and that the alligator "is the child's most primitive enemy because he represents oral aggression . . . both by the child and against him." Even if you took the authors' word for all this (the authors' word being the only proof offered), you are still entitled to the very pertinent, though slangy, question, "So what?" If the killings and beatings and bitings in the story do "represent" aggression, it would seem that the psychiatrist and puppeteers, repeating the fights over and over again and providing the alligator and the canni-

bals, are the aggressors much more than the children, who want the monkey and Casper to be friends, who want the monkey spared, and who warn Casper against imminent danger.

RELATIONSHIP THERAPY THROUGH PLAY

Almost all of the forms of "play technique" discussed so far were based on the desire to discover and release mechanisms, complexes, conflicts, and unconscious drives supposed to be dormant in the patient. Those hidden forces, deriving from the child's past, were to be brought to light through play. The investigators did so by matching the children's performances with a few numerically limited items from the psychoanalytic grab bag.

Contrary to the monotony and repetitiousness of such procedures, Frederick H. Allen[1-3] was one of the first to bring originality and soundness to play work with children. His presidential address, read before the American Orthopsychiatric Association, is a masterpiece both in style and content. It is the result of mature thought and genuine interest in children rather than theories.

Allen entertained no pretenses that he was "invested with certain omnipotent powers that sometimes are assumed by, sometimes assigned to, the psychiatrist." He said modestly: "Gradually I am coming to recognize and, what is more important, accept without apology my limitations in reshaping the feelings and behavior of another." He had no desire to impose his own standards on the patient: "The capacity to accept a child or adult as he is, without an urge to recreate him, or to take over his own responsibility for living, is indicative of my respect for his capacity to work on his own problem, or to achieve a healthier expression of himself through the type of relation I enable him to have with me as a therapist. . . . If I can create a relation in which the child . . . feels that he is accepted at the point he is in his own growth—rebellious, hostile, fearful, or what not—then that person has an opportunity to go ahead with those difficulties that are most concerning him. The main thing is that a patient has a relation with another human being to whom he has come, or to whom he has been sent, for help with problems within his own life." This relationship "comes to have value in and for itself, as a present reality which affords the patient a clarifying milieu, not as a representation of another person, past or present, but because of what he is experiencing with me at the moment."

For these reasons, Allen "stresses the value of play as providing the child with familiar tools to relate himself to the therapist. Into the play he will bring the reactions and feelings common to his relations outside. He will draw me into the play; he will shut me out; he will attempt to boss me; he will attempt to take away my toys, or to destroy them. . . . The actual content of his play becomes of less importance than the use he is making of it in relating himself to me. Interpretation then is in terms of the present meaning rather than in terms of the past."

Allen interviews the child for a set period, during which the child is allowed to play freely and spontaneously and, within reason, to do as he pleases. Difficulties which he experiences in doing so are discussed with him in terms of what is happening at the moment. Every sensible person will wholeheartedly agree with Allen when he says: "The human being is a growing, changing biological entity, not a machine consisting

of a mass of mechanisms; clinics must continue to be places for understanding human behavior and not become psychological garages."

Allen speaks rather contemptuously of the value of situational therapy. He does, it seems grudgingly, admit that "some knowledge" of the background will enable him to have a clearer understanding of the difficulties the child will have in relating himself to the physician. He deals almost exclusively with the child himself and abandons what goes on at home and at school to his social workers. But home, school, and neighborhood certainly cannot be left out of the therapeutic arrangement. No amount of relationship therapy will help a child who is in turmoil because of his father's alcoholic ranting, maternal overprotection and oversolicitude, or scholastic misplacement. "Understanding the child" is, of course, highly desirable. But a child needs help not only in "working on his problem," but also in having life made more comfortable and less problematic for him. The "psychotherapist" must not forget that this may include tonsillectomy, dental care, or the correction of a refractive error. Hence, Allen's scorn of "directive therapy" is quite unfair to those who cannot (and do not wish to) afford the luxury of selecting their cases to meet the indications for relationship therapy, and also unfair to parents who, whether they recognize it or not, need guidance, and to many children whose situational distress needs not less understanding "directive" relief from without.

There is not the slightest doubt that this type of treatment works well in the hands of Allen, whose kindly, warm, interested, and skilled devotion would help children with any method he may employ. But such things cannot very well be taught to others. There are people who think that all that is needed is to have a child come to the office for many hours and play around, with varying notions as to how far they should allow the patient to go in destroying toys, hitting the examiner, and carrying on otherwise. There are people who gain the impression, surely unjustified as far as Allen is concerned, that "free play" is welcomed as an "easy way"; you do not have to bother with parents, teachers, or the big and little entanglements of everyday life; you simply refuse to "accept" the feebleminded, epileptic, psychotic, and neglected children, and the offspring of parents who themselves need not remaking, but a great deal of direction. Some psychiatrists and, I am sure, all pediatricians take the children as they come and refrain from picking out a certain group of patients and relegating the others to whomever wants to have them.

OTHER FORMS OF SPONTANEOUS PLAY THERAPY

Rogerson,[41] working in the Child Guidance Clinic at Guy's Hospital in London, combined relationship therapy through free play with environmental adjustment. He emphasized the security which a child develops in his dealings with the therapist. He could find no reasonable justification for automatic Freudianization of the children's productions, though he is somewhat ambiguous about the so-called Oedipus situation. He thus explained the improvement which followed treatment in many of the "highly selected" cases: "1. It may be entirely spontaneous. 2. It may occur as a result of environmental manipulations. 3. It may be due to play therapy. None of these three possibilities alone will account for the facts; on the other hand, none of them

can be left out of consideration." In the play sessions, the child "could make as much noise as he liked, say and do what he liked, and in fact do anything except break the windows or lights."

Newell[38] reported similar work at the Baltimore Mental Hygiene Clinic.

This reviewer is greatly impressed by the marked contrast between the interpretive, at times arrogant, cocksureness of the psychoanalytic group on one side, and the humane, modest spirit of helpfulness of men like Allen, Rogerson, and Newell on the other side. Whatever the reasons for the reported improvement may be, the effect of kindliness, appreciation of what a child offers, and opportunity for free expression met with tolerance and good nature cannot possibly be left out of the account. This is a different atmosphere from one in which a child is constantly told that he wants to cohabitate with his parent of the opposite sex, swallow his father's penis, and tear his mother's body apart.

SITUATIONAL CONTENT PLAY

In contradistinction to standardized and spontaneous play methods, some investigators have attempted to adapt the play setting to actual life situations centered around the child's difficulties.

D. M. Levy[31, 32] introduced the method of "release therapy," by which is meant "a psychotherapy in which the primary concern of the therapist is to create or facilitate the creation of situations by the use of play methods in which the anxieties of the child are given expression." He distinguished two types of procedure. Specific release therapy "relies on various forms of restoring the situation out of which the anxiety and its accompanying symptoms arose." He was satisfied with the results: "In general, the experience with specific release therapy applied to symptoms arising out of a definitely known traumatic episode is quite gratifying." General release therapy "is utilized typically when symptoms have arisen in the child because of excessive demands or prohibitions made upon it at too early an age."

In this "controlled" play, "the therapist supplies the main actors and the dramatic situation. The child is encouraged to work with the plot selected, add whatever other actors or scenes he wishes, and keep the play going." In the selection of plots, however, Levy allowed himself quite often to depart from the child's real life situation. The plots were chosen with a bias, with an eye on what the experimenter anticipated a priori. A 2-year-old girl, referred because of general negativism, severe temper tantrums, lack of demonstrable affection, sulkiness, and tenseness, came unwillingly into the office. Levy took a gun, shot at some clay figures, and then said: "Who shall I shoot?" "She pointed to her mother, at whom I shot, and then at me." (Levy and the mother were the only two persons present.) The child then hid under a chair. She emerged with some difficulty and Levy threw various objects on the floor, hoping "to release her own destructive behavior by preceding it with my own performance." The therapist starts out by assuming the presence of hostility, aggression, sibling rivalry, certain anxieties, motivations, cause-and-effect relationships, and then proceeds to play with (and sometimes for) the child in order to bring out and "release" the assumed features.

Jacob H. Conn[10-12] has developed his method of "play interview" at the Children's Psychiatric Service of the Johns Hopkins Hospital. The play interview is not meant to replace, but to supplement, regulated pediatric-psychiatric examination and treatment. "It is not a fixed technique but an opportunity for the child to express himself and at the same time to reveal to himself the role which he has played in his illness. This is accomplished by providing an opportunity for the child to speak for each of a number of dolls, and simultaneously to view all that is going on while he is actively participating in an intimate discussion of his own attitudes. It is not the child but the doll who is afraid of the dark. It is not he who is envious or hates but the doll character. Therefore, he can give an account of the motives and imaginations which may explain the doll's behavior and consequently his own. Toy furniture and dolls representing various characters (parents, siblings, teachers, etc.) are used during the play interview, and various scenes are arranged by the physician as upon a miniature stage. In every case the realities of the child's life situation suggest to the physician what play experiments to set up.

"The play interview is neither a glorified free play period nor an invitation to release self-assertive, hostile tendencies. It is a seriously motivated, purposeful experience in which the child accepts the role of a collaborator, an equal, who comes to teach as well as to learn. It fosters a succession of significant decisions which are to be carried out in the interval between interviews, rather than a verbal exercise or a preparation for a later doing, which may be carried over into other situations in some mysterious manner.

"In contrast to the method of conditioning, which is a time-consuming, familiarizing process, the play interview offers the child an opportunity for an objectification and immediate reshuffling of perspectives. This usually occurs within one or two interviews, during which the child not only learns and accepts what he has contributed to the total situation, but for the first time finds himself secure in a personal relationship. He can, therefore, begin to develop the courage that comes from self-criticism, a sense of freedom arising out of self-expression, and be helped in the direction of happy, healthy living.

"The acceptance of a child for treatment is in itself a significant therapeutic fact. The much troubled parent finds someone to confide in who is willing to take over the responsibility for the care of her 'fearful' or 'nervous' child. This 'calling off the dogs' of criticism and nagging is appreciated by both parent and child."[13a]

The play interview, free of foregone conclusions or specific anticipations, makes it possible to learn from the child himself what is going on within him, over and above the rest of the examination which tells us what is and has been going on around him. There is no need to harken back to the past only or to remain in the present only. It is the child who, in his play, may spontaneously bring in experiences of the past and relate them to the present. The combination of work with the child, the family, the school, and, if necessary, the social agencies in behalf of the child gives reasonable assurance that the life situation will, to the extent possible, be made comfortable for him through "directive" measures and that he will be made comfortable in the life situation through the insights gained by himself and the investigator in the play interview. There is no exclusiveness in the

choice of help given; to give help is the main concern. Some of it may come from relationship with the therapist and through "self-direction," and some of it will have to come through experienced direction by the investigator and his collaborators on the basis of the total constellation and the child's attitudes learned in the play interview. Schematized "interpretations" hinder rather than enhance such helpfulness. Conn's efforts are decidedly noninterpretive and oriented practically toward adjustment of the child in the world in which he lives.

Two of Conn's pupils have published accounts of their work. Waterman[46] applied the play interview method to juvenile delinquents. Solomon,[44] who termed the procedure one of "active play therapy," spoke of it as offering "rapid diagnostic and therapeutic assistance in the emotional problems of childhood."

The play interview has indeed served not only as an aid to therapy, but has also opened new ways for topical investigation. This was best shown by Conn's study of ear sickness[9] and more especially by his investigation of the development of sex awareness and sex attitudes in children,[13] reported in last year's critical review of infantile sexuality.*

SUMMARY

Investigative, diagnostic, and therapeutic play work with children has, especially in the past five or six years, gained considerable attention in a number of centers. It has been used by psychoanalysts as one more excuse for foisting a limited set of one-sided and unproved "interpretations" on playing children. It has been used to bring out and release various tensions and anxieties in more or less standardized arrangements. It has served as a means of establishing a therapeutic relationship between physician and patient. It has been employed to give children the possibility to express themselves in a secure, tolerant atmosphere in a manner suited to them.

Play work with children, still in its beginning, has come to stay. The pediatrician will hear much about it in the next few years. This review is intended to give him a general orientation. Much haphazard and thoughtless toying around with children, with and without "interpretations," has of late been misrepresented as play therapy by uninformed and unskilled people. It is well for pediatricians to beware of such uninhibited intruders. It is also well to remember, and I hope that this review has made it clear, that therapeutic play with a child is not child's play.

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American Academy of Pediatrics

Proceedings

NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, OHIO—NOVEMBER 16-18, 1939

Round Table Discussion on the Therapeutics of Anemia

Chairman: Thomas B. Cooley, M.D., Detroit, Mich.
Assistants: Louis K. Diamond, M.D., Boston, Mass.
Hugh W. Josephs, M.D., Baltimore, Md.
Carl V. Moore, M.D., St. Louis, Mo.
Secretaries: Henry G. Poncher, M.D., Evanston, Ill.
Margaret M. Nicholson, M.D., Washington, D. C.

CHAIRMAN COOLEY.—The majority of the problems concerning the treatment of anemia have to do with the metabolism of iron and its effects on blood formation, so that the major part of any such discussion as this must deal with the uses of iron and of substances which may be considered adjuvants to iron therapy.

Dr. Moore will discuss basic facts in this field.

DR. CARL V. MOORE, ST. LOUIS.—While our understanding of iron metabolism is admittedly far from complete, experimentation during the past two decades has provided us with an infinitely more complete picture of the way in which the body handles iron. It is my function at this round table discussion to review these developments and to emphasize how they help to solve certain of the problems of iron therapy.

I. Factors Which Influence the Absorption of Iron.

A. Gastric Acidity.—Iron's first important stopping place as it begins its sojourn within the body is in the stomach. Recent work indicates that only ionizable iron can be absorbed from the intestinal tract. It apparently is one of the functions of the free hydrochloric acid of gastric secretions to ionize that portion of ingested iron which is capable of being ionized. A few years ago Dr. Elvehjem and his co-workers called attention to the fact that not all of the iron in food can be used for hemoglobin synthesis. Some of it is bound in such firm organic linkage that the gastric free hydrochloric acid cannot dissociate it from its chemical union. This portion is apparently not absorbed from the intestinal tract. Only that fraction of food iron which is ionized in the acid gastric juice is "available" for absorption. The percentage of ionizable iron in foods varies from about 20 per cent for some of the leafy vegetables to 100 per cent for egg yolk. This demonstration has more than academic interest in that it invalidates all previous estimations of the number of milligrams of iron which must be ingested each day

with our food to keep us in positive iron balance, and demands that these figures be restated in terms of milligrams of ionizable food iron. It had been shown previously that a similar explanation answered the question of the relative therapeutic value of inorganic and organic iron compounds. In the organic forms, iron is frequently bound in such a manner as not to be released or ionized under the physiologic conditions which prevail in the stomach and upper intestine. Hemoglobin and hematin are classic examples of this type of compound. The iron contained in them cannot be assimilated. However, there are other organic forms of iron—simple salts of iron with organic radicals like ferrous gluconate and ferrous glutamate—which are quite as therapeutically active, quite as readily absorbed, as are similar inorganic forms. The whole emphasis in the debate which occurred ten or more years ago about the relative efficacy of inorganic and organic iron in the treatment of the hypochromic anemias was incorrectly placed. It is important only that the iron be in an ionizable form; the inorganic or organic nature of its union is irrelevant except as it influences this property.

Gastric acidity, however, does more than aid in the ionization of food or medicinal iron. It helps to keep it in solution. Iron salts are precipitated as insoluble compounds when their solutions approach neutrality (above pH 5.0). This is particularly true for ferric salts, but, in association with other digesting foodstuffs, applies to the ferrous as well. Insoluble compounds are formed with phosphate, amino acids, proteins, etc. Normal gastric acidity prevents this change in the stomach and delays its occurrence in the duodenum.

B. Reduction and Alkalinization of Iron in Small Intestine.—When iron reaches the intestinal tract, it is subjected primarily to two influences: (1) the reducing action of the intestinal contents which tends to reduce any trivalent iron to the ferrous form; and (2) the alkaline intestinal juices which favor the formation of insoluble compounds as mentioned above.

The reducing action of the small intestine is of importance to this discussion because there is considerable reason to believe that iron is absorbed largely, if not entirely, in its ferrous form. This can probably best be illustrated with the use of serum iron absorption curves. These are produced by increases in serum iron which follow the ingestion of fairly large doses of soluble iron salts (4 mg. of elemental iron per kilogram of body weight) and are roughly comparable to glucose tolerance curves. The first curve in Chart 1 represents a characteristic response. You will notice that the serum iron value begins to rise within the first hour, reaches its peak in from two and one-half to five hours, and shortly thereafter begins to fall. The two left hand curves in this figure were produced in two different subjects by the oral administration of ferrous sulfate. Good evidence of absorption was obtained in both instances. When a comparable simple ferric salt, ferric chloride, however, was substituted, there was little or no response. The negative result does not necessarily mean that none of the iron in ferric chloride was absorbed, but it does indicate that the absorption was not nearly as great as with the ferrous salt. If strong reducing substances, however, such as cevitamic acid or sodium formaldehyde sulfoxylate, were given simultaneously with the ferric chloride, curves comparable to those produced by ferrous sulfate alone were obtained (Chart 1). In other studies, it was shown that, before iron and ammonium citrate would give the same elevation of serum iron as would a comparable quantity of ferrous sulfate or ferrous chloride, the dose, in terms of actual iron, had to be four times as great. These findings provide clear, objective confirmation of the clinical experience during the past few years that optimum therapeutic effect is provided by much smaller doses of ferrous than of ferric iron. This may mean that the iron of ferric salts must be reduced to the divalent state before it can be taken up by the intestinal mucosa.

The next question is this: If the intestinal tract can reduce ferric iron, then why isn't the absorption as complete as with ferrous forms? Explanation is

provided by the fact that the intestinal juices are also alkaline and begin to precipitate iron as soon as the reaction of the material delivered from the stomach has been raised to a pH of 5.0 or above. The precipitation of ferric iron is particularly prompt. Probably, therefore, only that portion of ferric iron can be absorbed which is reduced before it is precipitated. We are presented here with a second possible explanation for the greater absorption produced by divalent iron. The intestinal mucosa itself may be no more willing to accept ferrous iron than ferric, but does so because ferrous iron is precipitated less readily and is therefore available to it over a longer period of time.

EFFECT OF CEVITAMIC ACID AND SODIUM FORMALDEHYDE SULFOXYLATE ON SERUM IRON ABSORPTION CURVES.

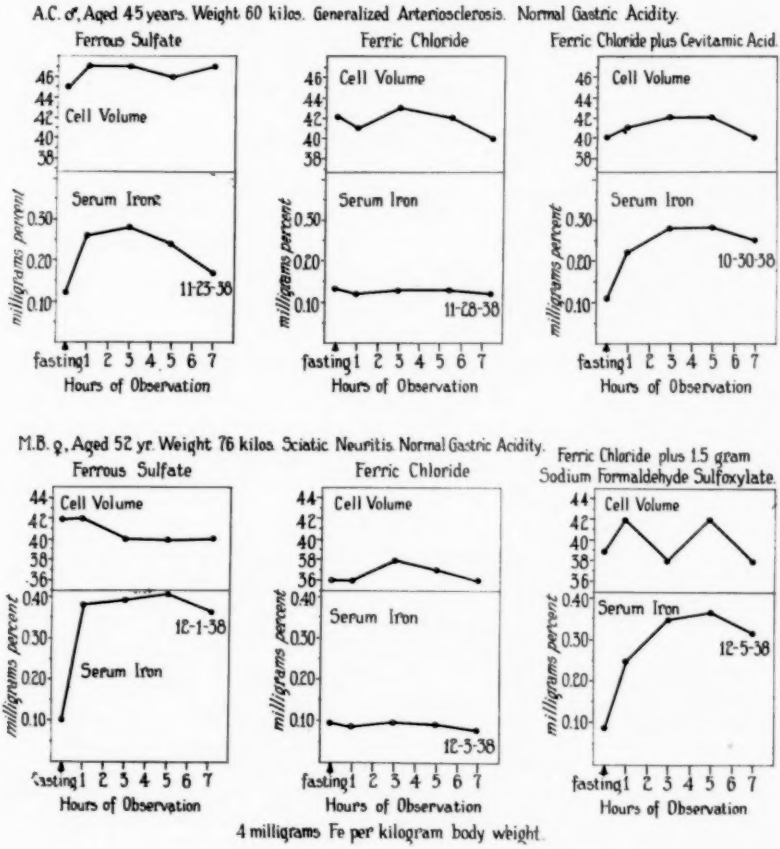

A.C. ♂, Aged 45 years. Weight 60 kilos. Generalized Arteriosclerosis. Normal Gastric Acidity.
Ferrous Sulfate
Ferric Chloride
Ferric Chloride plus Cevitamic Acid
Cell Volume
Serum Iron
milligrams percent
11-23-38
11-28-38
10-30-38
fasting 1 2 3 4 5 6 7
Hours of Observation
M.B. ♀, Aged 52 yr. Weight 76 kilos. Sciatic Neuritis. Normal Gastric Acidity.
Ferrous Sulfate
Ferric Chloride
Ferric Chloride plus 1.5 gram Sodium Formaldehyde Sulfoxylate
12-1-38
12-5-38
4 milligrams Fe per kilogram body weight.

Chart 1.

This concept of what happens to iron in the intestinal tract, while not proved, is probably fairly accurate. Not only does it offer an adequate explanation for the fact that ferrous salts are effective in much smaller doses than are the ferric, but it indicates why such large doses of iron are necessary in clinical practice.

Physicians and pharmacologists have been troubled by the fact that only from 3 to 5 per cent of administered iron is actually used for hemoglobin synthesis. Why, then, is it necessary to employ doses that are at least ten to twenty times greater than the amounts of the metal actually utilized by the body? The most logical explanation is provided by the simple phenomenon of precipitation. The iron solutions are probably changed so rapidly to a pH of about 5.0 after they reach the duodenum that only a very small proportion can be absorbed before the insoluble compounds are formed.

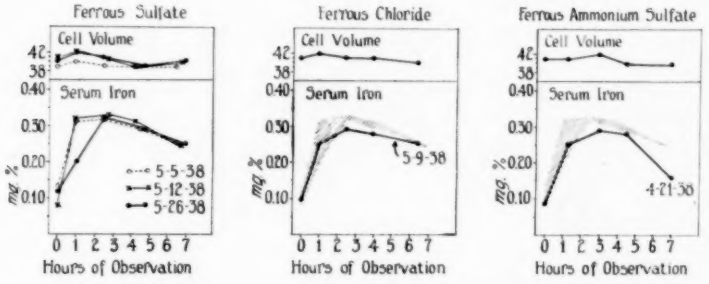
It has already been stated that ferrous and ferric phosphate are among the insoluble iron compounds formed in the intestinal tract. That this reaction has special significance has been pointed out by Dr. Diamond and others, for with it phosphates as well as iron become unavailable to the body economy and cannot be absorbed. It is theoretically possible that such large quantities of phosphate might be trapped in this manner as to disturb the normal relationship between calcium and phosphorus sufficiently to cause rickets. This result has actually been produced experimentally in laboratory animals, but to date no case of human rickets traceable to iron therapy and phosphate precipitation in the intestine has been recognized.

C. The Site and Mechanism of Absorption.—It is thought that the absorption of iron takes place largely in the duodenum. Observations have recently been completed in our laboratory which offer convincing evidence that the mucosa of the jejunum, and to a lesser extent, that of the ileum, is likewise able to participate in this assimilation process. It is not known, however, exactly how the absorption takes place. Some workers have postulated that iron merely diffuses into the blood stream through the intercellular spaces between the mucosal cells; others have concluded that the epithelial cells of the mucosa take an active part by ingesting iron just as they do lipid material. It has been suggested repeatedly that the anion to which iron is attached plays an important role in determining the absorbability of the metal. The statement has been made, for instance, that ferrous chloride is more completely or more readily absorbed than are other ferrous salts such as the sulfate or carbonate. If comparison is made, however, of the serum iron absorption curves produced by equivalent amounts of different ferrous salts, all seem to be absorbed equally well as long as they are equally soluble and ionizable (Chart 2).

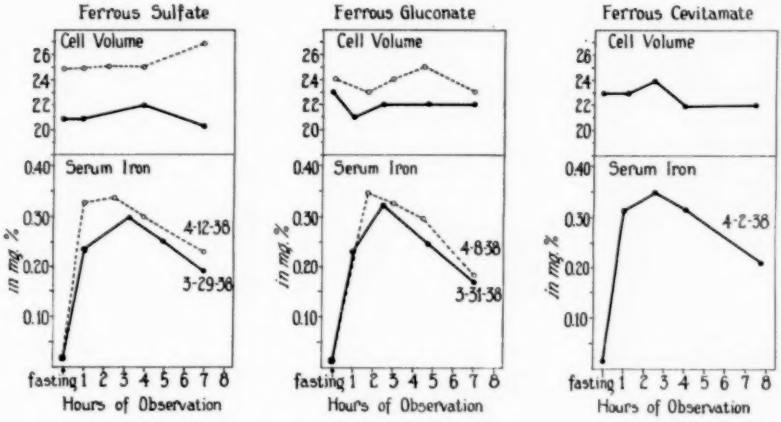
Intestinal pathology or irritation may interfere with iron absorption, particularly when it causes enough increased motility to sweep the iron digest mixture past the absorbing portion of the intestinal mucosa at a rate that is too rapid to permit optimum assimilation. During fever and general metabolic disturbances there is also diminished absorption of iron. Patients with advanced nephritis or with terminal leucemic manifestations have never shown significant increases in serum iron after large doses of iron salts by mouth. We have recently observed a patient with hypernephroma who had developed a severe hypochromic anemia because of renal hemorrhage for many months. During the period of her hospitalization, she ran a septic type of temperature curve with daily spikes to 39° C. or above. She was given ferrous sulfate orally in full therapeutic doses (0.8 Gm. daily) for several weeks, without showing any clear-cut evidence of the usual reticulocyte response. That the therapeutic failure was at least partly due to faulty absorption was evident from the fact that a good reticulocyte response followed the daily administration of iron intravenously as colloidal ferric hydroxide (32 mg. of elemental iron each day) (Chart 3).

D. The Adequacy of Iron Reserves.—The suggestion has repeatedly been made by various investigators that the intestinal mucosa might be able to accept or reject iron according to the needs of the body. This idea has been restated and crystallized within the past year by Hahn and Whipple, who postulate that this

willingness or refusal to absorb iron is one of the principal regulatory mechanisms of iron metabolism. When we analyzed the question of selective iron absorption with the serum iron absorption curve technique used in all our studies, we obtained, however, data of conflicting character. Some observations tended to confirm, others to deny, this possibility. It is difficult to believe that the cells



N. J. T., ♂, 49 years, histamine refractory achlorhydria.



G. W., ♂, 45 years, normal gastric acidity.

* 4 mgms. Fe^{++} as each of above salts per kilo body wt.

Chart 2.—Comparison of serum iron increases produced by different soluble ferrous salts.

of the intestinal mucosa can function so as to absorb selectively iron only when it is needed by the relatively distant organs of utilization and storage. Fowler and Barer, as a matter of fact, noted that several of their subjects, while taking 3 Gm. of ferric ammonium citrate daily, stored as much as 8 Gm. or more of the metal during a six-week period. This figure is made more significant when it is recalled that the circulating hemoglobin of the normal average adult contains only about 2.0 to 2.5 Gm. of iron. Yet it is true that iron-deficient persons will often show greater retention of iron than will normal persons. It is entirely possible that this results, not from any selective absorption by the mucosa, but rather from the greater rate at which iron might diffuse into the blood stream

when the iron in serum is low (as it is in the iron deficiency anemias). Since, however, the problem is wholly unsettled and has no obvious therapeutic implications, further consideration at this time does not seem necessary.

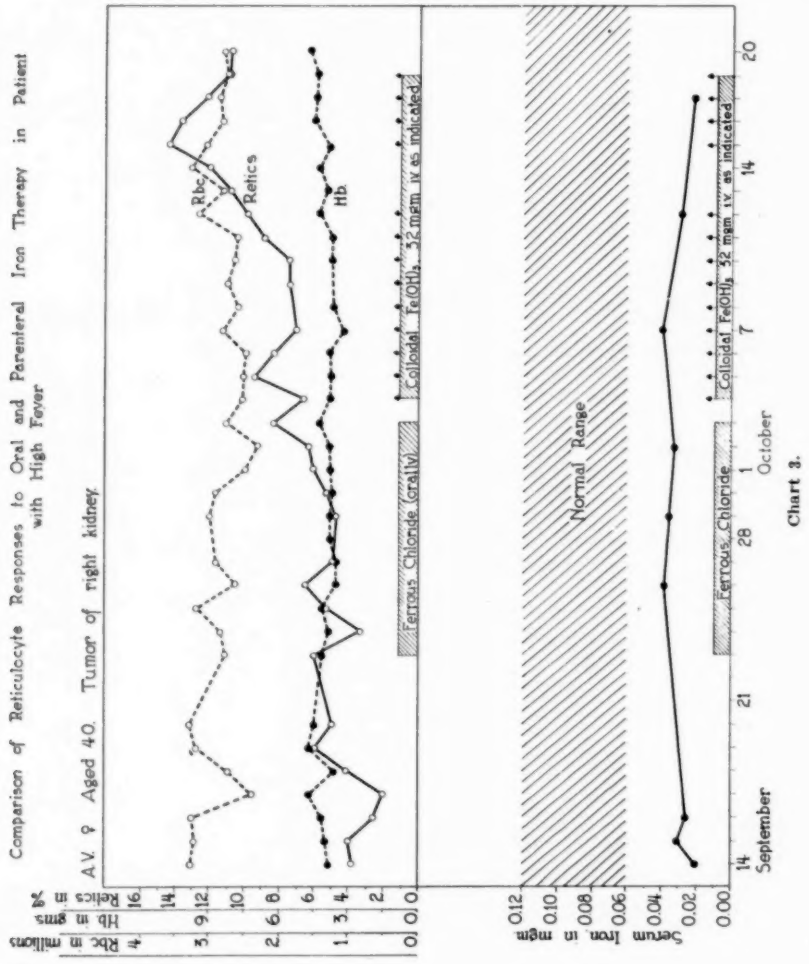


Chart 3.

II. Iron Transportation and Storage.

Iron is transported in serum or plasma and stored largely in the liver, spleen, kidneys, and bone marrow. The way in which iron is transferred from plasma to the organs of storage, the form in which it is deposited there, the cells chiefly responsible for the storage, and the mechanism of remobilization of iron are matters about which there is little exact information.

When the red cells which have completed their life cycle are destroyed either in the spleen or elsewhere, the hemoglobin released from them is broken down into globin, bile pigment, and iron. This iron is again transported in the blood plasma

to the organs of storage, utilization, and excretion. Normally, as a matter of fact, it is the body's major source of iron supply.

Pediatricians, of course, have a very good practical reason for being interested in the question of iron storage. It has been demonstrated that the iron stores with which the normal human infant is provided at birth are accumulated largely during the last trimester of pregnancy. Premature infants, therefore, are born without at least a portion of this reserve which normally helps to tide them over the first few months of rapid growth and low food iron intake, and this deficiency at least contributes to the development of nutritional anemia. Iron-deficient mothers, likewise, are not able to spare their fetuses all the iron that would be necessary to permit the full complement of prenatal storage. Infants born to them are more likely to develop severe anemias during the first year of life. But if iron therapy is begun in these mothers as late as the eighth month of pregnancy, the fetal iron stores are built up to approximate the normal before delivery at term occurs.

III. Factors Which Control the Utilization of Iron.

In discussing iron utilization, we must remember that iron not only serves as a component of the hemoglobin molecule, but is also present in myohemoglobin (the pigment of red muscle), in the nucleus of all cells, and in the respiratory enzymes. But for all practical purposes we are primarily concerned with the use of iron for hemoglobin synthesis. It may be stated parenthetically that we are fortunate that this is so since little is known about the factors which control iron metabolism in its relation to these other three functional associations.

ESSENTIAL FACTORS NECESSARY FOR NORMAL ERYTHROPOIESIS

I. Component parts of the erythrocyte
  A. Stroma of the red cell
    Lecithin, cholesterol, paraglobulin, nucleoprotein, etc.
  B. Hemoglobin
    Hemoglobin
    Heme — Globin (proteins, essential amino acids, etc.)
    Iron — Protoporphyrin (pyrrol nucleus)

II. Substances which stimulate normal erythropoiesis
  A. Endothelium
    ↓
    Vitamin B_c (?)
    ↓
    Megaloblast Erythrocyte Maturation Factor, Normoblast
    ⟶
    Iron, Vitamin C, Thyroxin, Erythrocyte
    ⟶

III. Catalysts or hemoglobin synthesis
  A. Copper
    Globin + porphyrin + Fe $\xrightarrow{\text{Cu (catalyst)}}$ Hemoglobin
  B. (?) Vitamin B_c (action unknown)

Chart 4.

A. Factors Necessary as Component Parts of the Erythrocyte.—For the sake of completeness, it is necessary to emphasize that iron could not be used for the manufacture of hemoglobin unless the other component parts of the hemoglobin molecule were also available. Similarly, the material from which the red cell stroma or membrane is made must likewise be present. These factors are summarized briefly in Chart 4. It is not certain, however, that any of them are ever

sufficiently deficient in the human being to be directly responsible for failures of iron utilization.

B. Substances Which Stimulate Red Cell Maturation.—The synthesis of hemoglobin apparently takes place within the developing red cell. If erythrocytes, therefore, fail to differentiate from endothelium in the bone marrow and a true aplasia of erythroid elements develops, no factory is provided for the putting together of hemoglobin, and iron is not utilized. Similarly, if the red cells fail to mature, the manufacture of hemoglobin is impaired. Summary of these relationships is included in Chart 4. It is interesting to note that many workers have suggested that iron may have some function to perform in helping to stimulate the maturation of the normoblast to the mature erythrocyte. The evidence in support of this statement is, however, by no means conclusive.

C. Catalysts of Hemoglobin Synthesis.—To most of us, liver and copper seem much more intimately related to problems of iron utilization, probably because they have been so widely used therapeutically in conjunction with iron. A number of years ago, Dr. Whipple and his associates observed that dogs made anemic by a systematic program of bleeding and fed a carefully standardized diet produced more hemoglobin when given liver and iron together than when given iron alone. The additive effect could not be explained on the basis of the extra amount of iron provided by the liver. This "secondary anemia" liver principle was precipitated by 70 per cent alcohol from an acidified aqueous extract of whole liver and could be concentrated in this manner. It is entirely distinct from the antipernicious anemia fraction. Its chemical nature and mode of action are unknown. Dr. Elvehjem has suggested that its effectiveness is due solely to the copper it contains, but this contention has been vigorously denied. Further discussion of the relation of liver to these problems, however, had best be left to Dr. Cooley, who plans to analyze the whole question of the therapeutic usefulness of liver as applied to the anemias of infancy and childhood.

Copper, without question, is necessary for iron utilization. The Wisconsin University group of investigators has shown that animals can absorb iron in the presence of a copper deficiency, they can store it, and they can mobilize it from the storage depots. But unless copper is present, they cannot use it for hemoglobin synthesis. The site of action of copper would seem to be in the bone marrow where it probably serves as a catalyst to make possible the assembly of the hemoglobin molecule. The practical necessity for using copper in the treatment of iron deficiency or hypochromic anemias as they occur in the human being, however, is by no means so clearly established. Since only minute quantities of copper are necessary, and since the metal is so widely distributed in nature, it is difficult to believe that copper deficiencies ever occur in the adult. It is unfortunate that chemical methods of analysis of sufficient sensitivity to establish or eliminate this possibility have not as yet been developed. We have observed a number of adult patients with hypochromic, microcytic anemia who received copper and iron together after they had first been given iron alone for a two- or three-week period. In no case was there a second reticulocyte response or any evidence of a more rapid hemoglobin regeneration. The limited diet of infants, however, makes it theoretically more possible for copper deficiencies to occur. A number of investigators have claimed more rapid hemoglobin formation with iron and copper combined; others claim to have observed additional rises in hemoglobin with copper after the response to iron alone had stopped. Since I am not a pediatrician and treat so few anemias in children, I hope that one of the other participants will add to this discussion. Dr. Josephs has written on the subject. It would seem a fair statement to say that probably not many children develop copper deficiencies. The routine use of copper and iron preparations seems unwise because of their greater cost. They should be reserved for those cases in which the response to iron alone is unsatisfactory.

Within the past year, Fouts and his associates have called attention to the relationship between vitamin B_6 and iron utilization. Dogs fed a B_6-deficient diet developed a hypochromic microcytic anemia which failed to respond to iron. When crystalline vitamin B_6 was given, however, there was prompt hemoglobin regeneration. The mechanism and site of action are not clear. No clinical recognition of this type of disturbance in iron utilization has yet been made.

D. Infection and Metabolic Disturbances.—Just as infections, fever, and metabolic disturbances interfere with the absorption of iron, so do they also interfere with its utilization. This can best be demonstrated with the use of parenterally administered iron. It has been claimed that iron-deficient animals or patients use injected iron quantitatively for the synthesis of hemoglobin so that there is a 100 per cent return. In the presence of an infection, utilization is much less complete. Dr. Robscheit-Robbins and Dr. Whipple observed this in their standard anemic dogs. The patient on whom the data in Chart 3 were obtained had a very satisfactory reticulocyte response to intravenous colloidal ferric hydroxide, but had only about one-third as much hemoglobin regeneration as should have occurred if utilization of the injected iron had been complete. There is no known way in which to alter this response except to treat the pathology which produces it.

IV. The Excretion of Iron.

The amount of iron excreted by the kidneys is very small. It was thought that the major responsibility for iron excretion was shared by the liver (bile) and by the colon. This was denied, however, in 1937 by McCance and Widdowson, who described experiments which tended to demonstrate that the ability of the body to excrete iron except by hemorrhage was exceedingly limited. Confirmation of these studies has come from two or three different laboratories. Hahn and Whipple carried the interpretation one step further. They postulated, as has already been stated, that, since iron-deficient animals seem to absorb iron less readily than do the normal, and since iron once in the body is excreted only very slowly, if at all, the body protects itself against overloading with iron by failing to absorb it except when needed. These ideas about iron excretion are not to be considered as having been established beyond question, but they must be accepted temporarily as part of our "working basis" conception of iron metabolism.

Out of this work has come one important clinical deduction. If iron is not excreted by the body in appreciable amounts, then iron deficiencies may develop only under two circumstances: (1) when there is rapid growth with increase in blood volume, as during infancy and childhood, and (2) in the presence of hemorrhage. Once a person has attained his full physical growth, poor dietary intake and poor absorption could not, in the absence of hemorrhage, cause a hypochromic anemia. This interpretation accounts admirably for the fact that about 90 per cent of all iron deficiency anemias in adults occur in women. Their menstrual loss keeps them in precarious iron balance. In rapidly growing children, however, there is need for additional iron as the blood volume increases and dietary inadequacies or poor absorption which interfere with the required assimilation of iron are of greater etiological importance.

Before this discussion is terminated, statement should be made of the fact that there are two, and only two, clinically recognizable criteria of iron deficiency: (1) hypochromia of the red cells, and (2) low serum iron (below 0.050 mg. per cent). The second is difficult to determine and is primarily reserved for use in clinical investigation. Tongue, fingernail, and mucous membrane changes are not sufficiently constant to be of much differential value. Hypochromia, then, must be the one outstanding phenomenon without which the diagnosis of true iron deficiency cannot be made. Many of the reported therapeutic failures attributed to iron are in reality not failures at all since iron is so often used indiscriminately in the

absence of hypochromia. It is not reasonable to expect replacement therapy to be of value unless there is need for the replacement. The one indication for iron therapy is the existence of an iron deficiency.

An abbreviated, schematic presentation of this outline of iron metabolism is made in Chart 5. It has been emphasized that our information is still far from complete and that interpretation of our collected data is often highly controversial. As the more complete story unfolds, it is to be expected that our present therapeutic methods will be altered and improved.

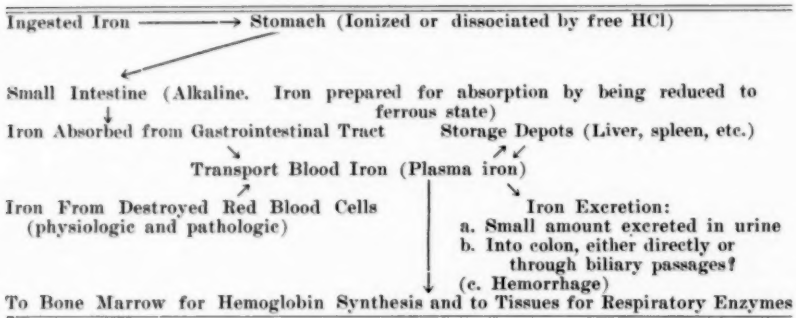

Ingested Iron
Stomach (Ionized or dissociated by free HCl)
Small Intestine (Alkaline. Iron prepared for absorption by being reduced to ferrous state)
Iron Absorbed from Gastrointestinal Tract
Storage Depots (Liver, spleen, etc.)
Transport Blood Iron (Plasma iron)
Iron From Destroyed Red Blood Cells (physiologic and pathologic)
Iron Excretion:
a. Small amount excreted in urine
b. Into colon, either directly or through biliary passages?
(c. Hemorrhage)
To Bone Marrow for Hemoglobin Synthesis and to Tissues for Respiratory Enzymes

Chart 5.

DR. L. K. DIAMOND, BOSTON.—Dr. Moore's comprehensive discussion of studies in iron transportation and iron metabolism has brought up the following interesting subjects which have important practical aspects.

1. Gastric Secretion in Relation to Anemia.—It has been known for a long time that infants and children with profound anemia require much larger doses of iron and seem to respond to iron medication less well than do adults. In many such cases, where gastric analysis has been carried out, it has been shown that such patients suffer from a relative achlorhydria, i.e., there is very little free hydrochloric acid in the resting sample of gastric juice and in the sample taken after test meal or alcohol ingestion. However, a moderately good response may occur after the subcutaneous injection of histamine. As proved by Dr. Moore, the administration of iron to such patients results in a poorer absorption of ingested iron. For this reason, larger doses of iron medication must be given to obtain an effect equivalent to that seen in patients without achlorhydria. As the anemia improves, the gastric secretion tends to improve and the achlorhydria disappears.

2. Index of Response to Iron Ingestion.—Although, as Dr. Moore has shown, a fairly accurate measurement may be obtained from serum iron determinations after the ingestion of various salts and foods containing iron, this newer method of study of iron absorption is not available to most clinicians and even to most hospitals. Likewise, Dr. Josephs' method of studying iron utilization by balance experiments with the patient on a metabolism bed does not lend itself to widespread uses. A simple and practical method of determining response to iron ingestion, either in medicinal preparation or in foods, has been carried out by us in the study of iron deficiency anemia. It is generally accepted that in iron deficiency anemia the ingestion of iron-containing substances leads to a specific response of the reticulocytes within from seven to ten days. The height of this reticulocyte peak is directly related to the amount of iron given and absorbed. Therefore, one can readily determine whether a minimal or optimal amount of the mineral has been ingested. The response is just as specific as that which occurs following the administration of liver extract to patients with pernicious anemia. By this

method we too have been impressed by the better response to ferrous than to ferric iron, as well as by the improvement following the use of soluble iron preparations in contrast to the insoluble forms.

3. Interaction of Iron and Phosphates.—Dr. Moore's studies have also confirmed an observation which was made by us several years ago and has been repeatedly confirmed since the original study. Just as it was shown that in animals the ingestion of large amounts of iron in the presence of a diet containing minimal amounts of phosphorus tends to induce rickets because of the precipitation of available phosphorus by the iron in the intestinal tract, the reverse has also been shown in animals, i.e., that large amounts of phosphorus and phosphorus-containing media will interfere with the absorption and utilization of iron in the intestinal tract. This has been proved in experimental study of infants and children with iron deficiency anemia. By following the reticulocyte response after the administration of iron, first in a phosphate solution, then in milk or with other phosphate-containing foods, and then either alone or in orange juice or some non-phosphate-containing diluent, it has been shown that the best response occurs when the iron is given not in association with phosphate-containing material. To obtain the most satisfactory response, therefore, iron medication should be given preferably between meals and not in milk. In this way the precipitating effect of phosphates on the iron will be at a minimum and the response to the medication maximum.

4. Dosage of Iron.—As to the dosage of iron in infancy and childhood, the general principles governing this are accepted by all of us. Simply stated, large doses of iron are necessary because: the growth of the child constantly dilutes the hemoglobin in the circulation and demands the production of much larger numbers of cells; iron is required in the growing muscle tissue as well as in the individual body cells, also constantly multiplying. In addition, the other factors mentioned heretofore, i.e., the tendency towards low hydrochloric acid secretion in the stomach of anemic children, the presence of large amounts of milk in the diet, all require increased iron dosage as compared to that ordinarily given adults. As Dr. Moore has pointed out, the justifiably favored iron medication at present is ferrous sulfate. This can be given in smaller amounts than iron ammonium-citrate or any ferric salt and, being readily soluble, is absorbed to a higher degree. To infants and children, this is generally given in solution in an elixir form and is very well tolerated. Roughly, the amounts of ferrous sulfate offered are as follows: To infants under 8 months, about 4 grains daily (2 teaspoons of elixir); between 8 months and 2 years, about 6 grains daily; between 2 years and 6 years, 6 to 8 grains daily; and between 6 years and puberty, about 8 to 10 grains daily. It is important to remember that some children develop gastric distress and vomiting and occasionally even diarrhea when the medication is first started. For this reason, it is safer to start with from a quarter to a half teaspoonful of the elixir, given once to twice daily between meals, possibly followed by fruit juice, and then to increase daily or every other day until the optimal amount is taken. Most children like the tart taste of ferrous sulfate and take it without any vehicle. If vomiting or diarrhea occurs, the medication may be omitted for a few days and then resumed in smaller doses, increasing until the tolerance is built up.

5. Infection in Relation to Iron Deficiency Anemia and Its Treatment.—Infection plays a very important role, both in the production and in the treatment of iron deficiency anemia in infancy and childhood. In this age group, infection occurs very frequently, and even when it does not specifically produce the anemia by hemolysis of blood or by toxic suppression of bone marrow activity, it interferes sufficiently with the appetite, as well as with the retention and absorption of necessary blood-building elements, to retard blood production. Also, as Dr. Moore has shown, infection interferes specifically with the absorption of iron, even when given in large amounts. It is futile, therefore, to treat children with anemia with iron administration during the course of acute infection or during the presence of a

chronic infectious state. Only after the infection subsides will iron be absorbed and utilized and blood regeneration become active. For this reason, it is well to withhold such medication until the child's appetite begins to improve or until all signs of residual infection have disappeared. Just when this moment arrives must remain a matter for individual appraisal in any given patient. As soon as indicated, iron therapy should be instituted in sufficiently large amounts and with sufficient regularity to produce maximum response of the blood. It should be continued until improvement is complete.

DR. H. C. CLARK, NEW ROCHELLE, N. Y.—Has the optimal dose of iron been determined?

DR. MOORE.—It is very difficult to make dogmatic statements about the optimal dose of iron. While from 50 to 75 mg. of elemental or actual iron given as one of the soluble ferrous salts is an adequate dose for an infant, it would take three or four times this much of the metal to produce the same satisfactory effect if it were given as a ferric salt. The reasons for this difference have already been stated. Perhaps Dr. Diamond or Dr. Josephs will be more definite. I feel it necessary to tread gently in discussing these specific questions about the clinical management of infants; they should be answered by pediatricians, not by an internist.

DR. JOSEPHS.—This has not been satisfactorily determined. The dosage that I have recommended for ferric ammonium citrate was the result of a determination of maximal reticulocyte response in a single case. From a recent study it is evident that, for most cases, a much smaller dose would be effective.

DR. CLARK.—Is the use of egg yolk practical in the prophylaxis of nutritional anemia? When should it be started?

DR. JOSEPHS.—I have no information on this subject. I have never felt that the nutritional means that we employ in prophylaxis offer any problem. However, I am coming to believe that nutritional factors are only a part of the story in the causation of "nutritional" anemia.

DR. MOORE.—Since egg yolk contains about 9 mg. per cent of iron, and since the average yolk weighs about 17 or 18 Gm., each egg has about 1.5 mg. of iron, all of which is ionizable. This amount needs to be supplemented, of course, with the iron in other foods, but it undoubtedly helps a great deal in protecting against the development of iron deficiency states in infancy.

DR. J. D. CRAIG, NEW YORK.—What causes pallor and anemia of children in the temperate zones, such as New York City? The diets of such children appear to be adequate in iron supply.

DR. JOSEPHS.—This is a good illustration of the fact that iron deficiency is only one of the factors in the production of anemia. One does not have to stretch the imagination to incriminate crowding, infections, lack of sunlight, and possibly other less evident factors occurring in a city in the winter. Ultimate purification of food and remoteness from the soil may introduce deficiencies which we do not yet recognize.

DR. L. F. HILL, DES MOINES.—At what level of hemoglobin can one say that anemia exists in full-term and premature infants, and when should iron therapy be started?

DR. JOSEPHS.—It is not possible to be dogmatic on this point. While it is probable that hemoglobin values between 10 and 12 Gm. per 100 c.c. (70 per cent to 80 per cent) are not harmful, it would probably be well to consider them evidence that the conditions were somewhat suboptimal. Since small amounts of iron are certainly harmless, there would be no reason for not giving iron in such a case.

DR. DIAMOND.—There is normally a low level of hemoglobin and red cells which occurs regularly between the eighth and twelfth weeks after birth. Ordinarily, in the normal healthy infant, at this time the red cell level may fall to about 4,000,000 or 4,500,000 per cubic millimeter and the hemoglobin level to about 11 or 12 Gm. per 100 c.c. or approximately 65 to 70 per cent. Without specific therapy, the hemoglobin and erythrocyte levels slowly rise during the following four to five months until the so-called normal of 4,500,000 red cells per cubic millimeter, and 13 to 14 Gm., or 80 per cent or better, of hemoglobin, are reached. This so-called physiologic anemia is not associated with any symptoms of deficiency such as pallor, poor appetite, poor digestion, lack of activity, or any evidence of ill health. It, likewise, needs no specific therapy in the form of iron or iron-containing foods. However, if the infant (1) is prematurely born, or (2) is one of twins or multiple births, or (3) is the offspring of an anemic mother who has not endowed her child with sufficient stores of iron during intrauterine life, or (4) suffers from repeated infection or digestive disturbances, this "physiologic" anemia may become accentuated and much more profound and extend beyond the sixth month or even the first or second year of life. In such instances, therapy is indicated, and large doses of iron are necessary to relieve the relatively severe hemoglobin deficit as well as possible erythrocyte reduction. The dosage of iron naturally depends on the age of the patient, the severity of the anemia, and the other factors that have been mentioned previously.

DR. JOSEPHS.—Perhaps a few detailed remarks about the anemia of prematurity should be made at this point. The course of the red cells and hemoglobin in premature babies falls into three roughly defined periods: (1) That from birth to about the end of the second or third month; (2) that from the third to the sixth month; (3) after the sixth month. In each of these periods the underlying factors are somewhat different, with the result that anemia occurring in one period will differ from that in another. It is well to understand this, for statements made about one period will not hold for another. In the literature, the term "premature anemia" is made to cover all three periods indiscriminately, with resulting confusion.

The first period is that of adjustment from the high level at birth to the lower level of extrauterine life. The reduction in hemoglobin and red cells, which is a purely physiologic phenomenon, is accomplished partly by an increased rate of blood destruction and partly by a slowing down of hematopoiesis. As the hemoglobin approaches a level at which stabilization is expected, the rate of formation ordinarily increases to the point at which it maintains the red cells and hemoglobin at the level we call normal. Often, however, this resumption of hematopoietic activity may be delayed somewhat, with the result that the red cells and hemoglobin fall temporarily below the "normal" level. This is the so-called physiologic anemia occurring at about the end of the second month of life. In the premature baby this resumption of hematopoietic activity tends to be more delayed than in the full-term baby, so that the resulting anemia is likely to be more severe and to last longer.

During the period when the hemoglobin is falling, the hematopoietic tissue is apparently refractory to stimulation. This should not be looked upon as abnormal, but merely as a result of the normal mechanism whereby the red cells and hemoglobin are brought down. The anemia at the end of this period is not due to nondeficiency. No form of therapy yet tried can be counted on to delay the fall in hemoglobin; but once the hemoglobin has reached its low level and the hematopoietic tissue is ready to resume normal activity, then stimulation will be effective. The fact that iron therapy provides such stimulation with consequent rise in hemoglobin does not mean that nondeficiency is a factor, for it has been shown that liver is just as effective at this point.

The second phase in the course of hemoglobin, that from 3 to 6 months, is marked by a gradually falling color index. While exogenous factors play an in-

creasingly important part in this period, it is probable that the falling color index is dependent principally on the gradual exhaustion of iron stores during a period of rapid growth. This is a true nondeficiency anemia which is dependent on prematurity only because, in the premature baby, the iron stores present at birth are not likely to be sufficient to support the relatively greater gain in weight. It differs in no respect from that of full-term babies who, for some reason, are born with deficient iron stores. In the absence of infection, and sometimes in its presence, iron therapy is effective.

While the anemia of this 3- to 6-month period may be more marked than that of full-term babies living under suboptimal conditions, it is by no means present in all, or even in a majority, of the premature infants, and it is rarely severe. The really severe hypochromic anemia occurring in twins and premature babies is not ordinarily encountered until the second half year, differs in no way from the severe hypochromic anemia occurring later in full-term babies, and is usually considered to be of nutritional origin. Recently, doubt has been thrown on the exclusive importance of iron deficiency in causing this type of anemia. There can be no doubt of the effect of iron therapy; the response is the same whether or not the baby was born prematurely.

The question may be asked, What is to be considered the anemia of prematurity? It is coming to be felt that the term should be reserved for those cases in which there is evidence that the hematopoietic tissue does not resume its normal activity at the end to the "physiologic" period, since such a failure is more directly attributable to the prematurity than is any other of the factors to which anemia occurring in premature babies may be attributed.

DR. A. S. HARDEN, JR., MAPLEWOOD, N. J.—What degree of fever or severity of infection would raise the barrier to the efficient absorption of iron from the intestine?

DR. MOORE.—It is not possible to give anything like an exact answer to Dr. Harden's question. The infection, in order to interfere with the absorption of iron, would have to be severe enough to produce a generalized systemic reaction. That is, an asymptomatic apical abscess or a chronic sinusitis should not do it. With our technique for studying absorption, we have observed increases in serum iron in the presence of a low-grade fever of from 99 to 99.5° F., but have never yet obtained an increase in a patient with an infection severe enough to raise his temperature above 100° F. These are not absolute relationships. There must be tremendous individual variations.

DR. CRAIG.—Following infection, how quickly does iron absorption or marrow activity return to normal? How soon may effective iron therapy be started after acute infection?

DR. MOORE.—That must vary greatly from patient to patient, and probably depends somewhat on the duration of the illness. We have made some observations on patients in whom fever was induced. Many of these showed no evidence of iron absorption. When several of these persons were restudied after one or two days, however, they again developed satisfactory serum iron absorption curves. I should imagine that iron therapy becomes effective rather promptly after acute infections.

DR. M. P. BOROVSKY, CHICAGO.—In a prolonged infection, what method is used to bring up the iron?

CHAIRMAN COOLEY.—Marrow utilization is very low in infection, so drug therapy does not aid. Transfusion is the only reliable method. Also hemolysis occurs during infection. When the infection has subsided, the marrow resumes its activity. Good response is obtained from hygienic care.

DR. W. F. BURDICK, WASHINGTON, D. C.—Elixir of feosal given between meals will cause nausea and vomiting.

DR. DIAMOND.—There is distress for a few days, but then it will be all right. Hence, start with a small dose. Three teaspoonfuls is equal to 6 grains. Start with ¼ teaspoonful twice daily, and at the end of six days you can work up to the full dose.

DR. JOSEPHS.—Do you give it to infants the same way?

DR. DIAMOND.—Yes.

CHAIRMAN COOLEY.—Next to iron, of the drugs now in vogue as antianemics, liver seems to hold first place, whether as an extract or as the cooked liver substance in which the laity have such faith. The extensive experimentation with liver therapy was based primarily on its success in pernicious anemia, and, although in other types its good effects may depend on quite different principles than in this disease, I think we must admit that it has earned an important place.

We can think of liver as playing two possibly distinct roles—first, as an adjuvant to iron in hemoglobin building, either by some synergistic action with iron, or by something needed for the protein part of the hemoglobin molecule. Whipple apparently showed that the effect of iron and liver given together was greater in increasing hemoglobin than the sum of the effects of the two given separately. Second, when there has been much hemolysis, or a period of cell aplasia, cell replacement is necessary and may be furthered by "building stones" stored in the liver which may be needed for cell structure. Here again we are indebted to Whipple, who showed in an interesting set of experiments that the livers of patients who, for long periods, had been unable properly to synthesize hemoglobin contained large amounts of substances favoring rapid blood building in dogs. Lacking specific information as to what these substances are and just how they operate, we may yet make some fairly justifiable assumptions. We know the liver is the chief depot for iron and copper storage, and that it seems to be the place of manufacture of several important nitrogenous constituents of the blood plasma; and it is not unreasonable to suppose that it may furnish amino acids or other compounds needed either for cell structure or for the protein part of the hemoglobin molecule which are not readily enough available from other sources for rapid use. We seem to be just at the beginning of the sort of intensive study of the amino acids which may give us information on these points. Whatever the theoretical explanation may be, both experimental and clinical evidence seem to indicate that, in nearly all conditions except those which may be classed as pure iron deficiency, liver is likely to be a valuable adjuvant to iron therapy.

There is some question as to the correctness of what seems to be a rather general assumption that whatever in liver is responsible for its effect in the "secondary" anemias is the same "maturation factor" which acts in pernicious anemia. I am not aware of any sufficient evidence for or against this view, but one must admit the possibility. A priori, I should be inclined to think it more likely that liver contains more than one of these "building stones" than that there should always be a deficit of the same substance in the different types of anemia in which liver is beneficial. Another possibility must be mentioned, viz., that in some of these conditions the copper content of liver, which is not inconsiderable, may play a part. We lack definite proof on this point.

Be these things as they may, we believe liver to be useful in addition to iron in most of the important anemias except the pure iron deficiency cases. In our clinic we used for some years a preparation containing a small dose of iron and ammonium citrate combined with an extract of whole liver and some probably quite superfluous condiments. With this mixture we had, it seemed to us, per-

fectly satisfactory results whenever a cure was at all to be expected, judging by rapidity of hemoglobin restoration and the dosage of iron necessary, which never reached the large amounts often given. More recently we have been using a slightly stronger solution of ferrous iron given orally, adding liver extract intramuscularly when it seems desirable. This also is satisfactory, although, as the preparations available for intramuscular use are those especially designed for effect in pernicious anemia, this might seem to militate against the idea that factors than the maturation factor may be involved. It is true also, I believe, that there is more copper in the pernicious anemia fraction.

We believe, then, that liver is a valuable adjunct in the treatment of a variety of anemias, particularly of the postinfectious types, but we are not yet certain of the active principles.

DR. R. A. HIGGONS, PORT CHESTER, N. Y.—What amount of raw liver is necessary in the diet?

CHAIRMAN COOLEY.—I do not know. I use extract entirely.

DR. JOSEPHS.—Give 5 c.c. per kilogram of body weight for a premature infant.

CHAIRMAN COOLEY.—Dr. Janet Vaughan has published a paper on this.

Question.—Is liver extract ever necessary, either alone or in conjunction with iron, for the treatment of anemia in infancy and childhood?

DR. DIAMOND.—For the ordinary simple iron deficiency anemia, iron medication alone in sufficient dosage produced a satisfactory response. However, as so frequently happens, where one deficiency exists, multiple deficiencies may be found. If, therefore, the patient fails to respond to iron alone, when given an adequate amount, or if there is a severe red cell reduction, both of which may indicate the need for an additional hematopoietic stimulus, whole liver by mouth or liver administered parenterally may be used.

One other point in this connection: Although the condition is very rare, occasionally a true macrocytic hyperchromic anemia occurs in infancy or childhood. We have seen about a dozen such cases in the last six to eight years (in comparison with many hundred iron-deficiency anemias). The discoverable causes for such a macrocytic anemia in infancy and childhood are as follows: (1) infection in the small intestine interfering with either the absorption or utilization of the intrinsic principle present in liver or in digestive products similar to liver; (2) congenital atresia or other gastrointestinal abnormality producing the same effect; (3) postoperative gastrointestinal shunts also interfering with the absorption of the liver extract principle; (4) disease of the liver interfering with the storage of this important material; (5) occasionally a *temporary* complete achlorhydria, as has been proved in a few instances where, apparently, the same mechanism for the production of macrocytic hyperchromic anemia exists as is present in the true pernicious anemia of the adult. In all these instances the administration of liver extract intramuscularly is followed by a prompt reticulocyte response, and with sufficient dosage, by a cure of the anemia, and usually it has not been necessary to continue this medication. Apparently the body is able to resume proper manufacture of or assimilation of the liver extract principle once the anemia has been relieved. Of course, this does not hold true in the cases of congenital malformation of the intestinal tract or postoperative shunt where the lesion cannot be remedied and continual parenteral liver extract administration may become necessary. Fortunately, such instances are extremely rare.

DR. JOSEPHS.—Transfusion is too broad a subject to be covered in a short time. I shall confine myself, therefore, to certain phases of the subject that seem to have received little discussion, and I shall say little concerning general indications.

The phases that I wish to speak of are those concerned with effects other than what may be called blood replacement.

It is, of course, nothing new that transfusion has other uses than the mere replacement of blood. Its beneficial effect in pneumonia, in chronic infections, and in chronic nutritional disturbances, is too well known to require recapitulation. Likewise, in purpura and other hemorrhagic diseases, the rationale depends on increasing the supply of material taking part in the clotting mechanism. In the case of anemia, however, the reason for giving transfusion has been first to raise the hemoglobin by supplying well-filled red cells, and it seemed worth while to examine the effect of transfusion in the anemias to see whether there were not effects other than replacement that deserved study.

In the hypochronic group, at first glance, the effect of transfusion appears to be explicable merely by the addition of so many red cells and so much hemoglobin. It is possible to calculate the expected rise in hemoglobin with a good probability that the actual rise will agree. But the hemoglobin goes on rising, i.e., something has been changed and hemoglobin is now formed where hemoglobin was not formed before. This may be a mere by-effect of replacement. There may have been a vicious circle, i.e., anemia may itself interfere with the synthesis of hemoglobin, and raising the hemoglobin may by itself restore normal conditions. But the possibility remains that the transfused blood contains something besides red cells that may play a part in restoring normal conditions. This is a point that might be studied profitably, and in studying it we might learn something of why babies become anemic.

In the aplastic-hypoplastic group of anemias, the effect is often rather difficult to explain. In the rare congenital cases the effect comes nearest to that of simple replacement; these children may live entirely on the blood that is given them, being completely unable to make any of their own. Also, in some of the chronic and not very severe cases, transfusion may tide them over temporary exacerbations without exerting any demonstrable effect on the underlying process. But in other cases it is not possible to explain the effect so simply. Not infrequently after a transfusion, the red cells and hemoglobin may be just where they were before the transfusion, or even lower, and urobilin excretion determination may demonstrate destruction of the transfused blood; yet often the patient shows improvement, and there may even be a temporary remission in the disease. One tends to explain such a phenomenon along familiar lines and to say that transfusion has aided the body's defense against the infection that is probably the underlying factor; but, as in the case of hypochromic anemia, an investigation of this effect may be profitable. For instance, in a case of congenital aplastic anemia, the only appearance of reticulocytes during a long course of observation followed a transfusion.

Several years ago I became interested in the effect of transfusion in sickle-cell anemia, for in that disease the rate of hemolysis is so great that the amount of blood destroyed in a day is often greater than any amount that could be given by transfusion. Moreover, it may often be observed that after a transfusion, the red cells and hemoglobin continue to rise for a period of two or three weeks, then gradually return to the original level. When the total urobilin excretion was studied, it was found that transfusion was followed by a marked fall in urobilin which lasted about as long as the amelioration of the anemia. It was next found that plasma had the same effect as whole blood, and then that, when the plasma was freed of protein and concentrated in vacuo, the effect was still present though not quite as marked or as constant. Evidently there is something in normal plasma that reduces the rate of hemolysis in sickle-cell anemia. Similar results were obtained in cases of congenital hemolytic jaundice. In general, the results are too inconstant to form the basis for treatment at present. The principal interest lies (1) in a possible light on the nature of the defect in sickle-cell anemia and congenital hemolytic jaundice, and (2) in providing a start in explaining an effect of transfusion that previously was rather obscure.

Before leaving the subject, I might say a word about two conditions in which it has been claimed that transfusion provides a specific cure, namely, acute hemolytic anemia and anemia of the newborn infant. In acute hemolytic anemia it is doubtful if transfusion is a cure in the sense of affecting the underlying cause; but there seems to be no doubt that those patients receiving transfusion recover more promptly than those allowed to recover spontaneously. The acute process is generally short-lived, and in some of the reported cases spontaneous recovery has been prompt; but in others spontaneous recovery is delayed, and transfusion has eventually been necessary. In the case of anemia of the newborn infant, it is likewise likely that transfusion has the function of maintaining life until the underlying process is at an end. When this has occurred, usually after three or four weeks of life, then transfusion may hasten a recovery that might be delayed without it.

DR. OTTO GROB, DETROIT.—What is the theory of aplastic anemia?

DR. JOSEPHS.—I do not know. In infections such as brucellosis we see an aplastic anemia, but in most cases no infection is found. It begins with joint pains, fever, etc., so it acts like an infection in some cases.

DR. MOORE.—Hypoplastic anemia is mysterious when you compare the bone marrow with the blood.

DR. JOSEPHS.—In your cases were there reductions of red blood cells and platelets?

CHAIRMAN COOLEY.—Rosenthal said many years ago that you might have a constant deficiency in any single element of the blood. I tried adrenalin without results.

DR. DIAMOND.—I applied x-ray to the long bones and the chest, but did not try adrenalin.

DR. GROB.—In acute hemolytic anemia, how low do you let the hemoglobin drop before giving a transfusion?

DR. JOSEPHS.—In the case we had, 105 per cent was obtained on admission, and it dropped to 85 per cent (12 Gm.) by morning. We waited until the next day to give the transfusion and the patient died.

CHAIRMAN COOLEY.—If there is a rapid drop, transfuse before a level of 8 Gm. is reached. In a chronic case, however, you can let it go much lower because there is no shock.

DR. DIAMOND.—I have been asked to discuss the conditions for which splenectomy has been advised. During the past twelve years material has been collected in our clinic from the study of infants and children for whom splenectomy was advised. The following diseases are found in this group:

1. Mediterranean anemia
2. Aplastic anemia
3. Splenomegaly with early hematemesis
4. Thrombopenic purpura
5. Splenic anemia
6. Gaucher's disease with splenomegaly
7. Congenital hemolytic anemia

Each of these will be discussed briefly:

1. *Mediterranean anemia,* or Cooley's erythroblastic anemia, often leads to the development of a very large spleen. This congenital and familial disease has

been recognized as an entity only since the original excellent description by Dr. Cooley. Because hemolysis was an active part of the picture, splenectomy was advised and carried out in quite a few cases many years ago. It was soon found that, following this operation, not only did the patient's anemia fail to improve, but it usually became more profound, and the numbers of nucleated erythrocytes in the peripheral blood rose tremendously. Often, one would find a level of from 300,000 to 400,000 of these cells per cubic millimeter after splenectomy, whereas, before the operation, a level of from a few hundred to a few thousand was the rule. The patient so treated succumbed to anemia, infection, and cardiac decompensation just as rapidly as did the unoperated patient. Since it has become evident that the patient does not benefit from the operation, and may be even more handicapped by the high level of erythroblasts in the circulating blood, splenectomy is contraindicated in this condition.

2. *Aplastic Anemia.*—The diagnostic criterion for this disease is a progressive anemia relapsing after transfusion, with little or no evidence of regeneration of erythrocytes. Frequently, the leucocytes and thrombocytes are likewise deficient in number. In physical examination, besides the extreme pallor, there should be absence of adenopathy and splenomegaly. The heart may show a variety of murmurs, as well as increase in cardiac size, and secondary decompensation may develop with increasing anoxemia.

Drug ingestion and exogenous or endogenous toxemia must be ruled out always since these so commonly lead to secondary aplasia of the bone marrow. In this connection, amidopyrine and its derivatives, benzol and benzol compounds, and radioactive paints should be sought. Infections and toxins of infections may be active even long after the acute manifestations have disappeared.

The essential laboratory data consist of a profound anemia with a color index of unity, often a leucopenia, frequently a thrombocytopenia, absence of reticulocytes, absence of icterus or increase in urobilin. When the erythrocytes alone are involved, the prognosis is more hopeful than when all the elements of the bone marrow are depressed.

The pathology may vary from the finding of a hyperplastic bone marrow which is functionally inactive to a hypoplastic condition in which there is only moderate absence of marrow tissue to complete aplasia, in which the erythropoietic centers are replaced either by fat or by fibrous tissue. Bone marrow biopsy is often necessary, not only to differentiate between these, but to rule out leucemia and other malignancies invading the bone marrow.

The complications of the disease are sudden collapse due to cardiac dilatation or slowly developing cardiac decompensation with terminal pneumonia. When leucopenia is marked, secondary infection of the skin, and especially of the mouth, leading to ulcerative stomatitis, is frequent.

Spontaneous remission may occur in all types of aplastic anemia, although it is least frequent in the cases where a sclerotic marrow is demonstrated. Medical therapy which implies the use of all the known stimulants to bone marrow activity should be tried. As a supportive measure and to prevent anoxemia and cardiac damage, transfusion should be given as often as necessary. In our cases, if no progress has been noted over a sufficiently long period of observation, or if transfusion becomes difficult, or if the patient does poorly in general growth and development, splenectomy has been attempted in an effort to produce a remission.

3. *Splenomegaly With Early Hematemesis.*—In all probability this clinical description fits the disturbance which is described pathologically as thrombophlebitis of the portal or splenic vein, or both. We have endeavored to differentiate this condition from classical Banti's disease of splenic anemia by the fact that, in splenomegaly with early gastric hemorrhage, there is a sudden onset of hematemesis or of melena, usually as the first sign of any abnormality in the patient. In addition to this, the diagnostic criteria include splenomegaly which gradually

increases between attacks of bleeding and persist until hemorrhage occurs, at which time the spleen shrinks until it is no longer palpable. Often, the history indicates either omphalitis in childhood or an intestinal infection or some other cause for obstruction to the splenic or portal system. By roentgenograms, esophageal varices may be demonstrated.

The laboratory data include anemia occurring only after hemorrhage, dependent upon the amount of blood lost, and, therefore, not constantly present. The reticulocytes, leucocytes, and platelets are increased after hemorrhage, indicating good bone marrow function.

Pathologically, there may be either extrinsic or intrinsic causes for obstruction to the portal vein. Among the former are tumors, enlarged lymph nodes, and congenital malformations. Among the latter are residual congenital valves in the veins, antenatal infection, and infections later in life. The resulting obstruction leads to the development of a collateral circulation, splenomegaly, and eventually varices in the stomach or esophagus which may rupture and cause hemorrhage.

Complications of this disturbance are the crises of abdominal pain which may be due to extension of thromboses and often lead to the diagnosis of an acute abdominal condition requiring surgical exploration. Hemorrhages may be so severe as to lead to exsanguination and death of the patient. This is particularly true if much of the blood enters the lower intestinal tract where it cannot be measured and if it is not replaced with sufficient promptness or in sufficient amount.

Splenectomy was advised at first merely for the removal of the enlarged spleen which was thought to be a burden to an obstructed circulation. However, as the result of this operation alone there was very little improvement, and more recently an attempt has been made to search for the site of venous obstruction and to try to remedy this. When this cannot be carried out, an attempt has been made to ligate the obvious varices and to assist in the establishment of a collateral circulation, chiefly by omentopexy. In our cases, the combination of splenectomy, ligation of dilated veins, and omentopexy has resulted in a better subsequent course for patients so treated. An interesting feature has been the improvement in girls with this disease after puberty. Apparently it is associated with the establishment of additional collateral circulation through the pelvic veins.

4. *Idiopathic Thrombopenic Purpura.*—It must be emphasized first that thrombopenic purpura with hemorrhage occurs much more frequently in childhood than in adult life as the result of infection, acute or chronic, evident or latent, even very slight and not affecting the patient's general health; drugs, such as the arsenicals, benzol and its derivatives, and mercury; and allergy. Careful exclusion of these etiological agents has gradually diminished the number of cases diagnosed as idiopathic thrombopenic purpura to a ratio of about one (idiopathic) to three (secondary). Obviously, the secondary type requires the most active treatment to eradicate the cause of the condition, and no surgical interference is necessary here.

In diagnosis, the finding of petechiae, ecchymoses, and free bleeding, splenomegaly often so slight as to be demonstrable only by weighing the organ, pallor and anemia dependent only upon blood loss, are all characteristic of the disease.

The laboratory data include thrombocytopenia, prolonged bleeding time, poor clot retraction, and leucocytosis and reticulocytosis in response to hemorrhage.

The complications result from the prolonged bleeding tendency, often precipitating hemorrhage, particularly in younger children who cannot be guarded against trauma. Slight trauma to the head, for example, may cause serious intracranial bleeding. Exsanguinating epistaxes may likewise accompany relatively slight trauma. In girls reaching puberty, prolonged menses may be very difficult to control and may lead to a serious state of anemia.

It should be remembered that the level of blood platelets is only one factor in prolonged bleeding or a tendency to bleed, so that the platelet level in itself may not indicate the amount of difficulty any given patient may experience.

Roughly, three of every four patients with idiopathic purpura seen by us have recovered spontaneously within from twelve to eighteen months after the first visit. In an effort to induce a remission, various medical measures have been tried. These include a high vitamin diet, liver usually in the form of whole liver taken by mouth, and x-ray therapy of the long bones, particularly in small repeated doses.

Recently, the induction of hypercalcinemia has been advised since, occasionally, toxic levels of calcium in the blood have induced a rise in the platelet level. To produce this, large amounts of calcium by mouth, in addition to tachysterol (Winthrop Co., A.T.10) or parathyroid extract intramuscularly, have been tried. Transfusion as frequently as necessary may not only control hemorrhage or improve anemia, but may also occasionally be followed by a spontaneous remission.

As regards splenectomy, this should be delayed until the purpura has become chronic (more than eighteen months in duration), or until repeated and severe hemorrhages necessitate an attempt at some therapy other than mere transfusion. In the child who is poorly cared for and subjected to much trauma, splenectomy may be necessary to avoid fatal injury, particularly from an intracranial hemorrhage. Finally, in girls after puberty, exsanguinating and repeated menstrual hemorrhages may require relatively early operation. In all these cases, splenectomy is usually followed by a rapid rise in the number of platelets to a normal level within a week, and persistence of this normal level thereafter. Occasionally, a relapse may occur, with a fall in platelets to the former thrombopenic level. Still more rarely, following splenectomy, there may be no rise in the platelets whatever, and the patient may be only slightly, or not at all, improved.

5. *Splenic Anemia.*—In contrast to the condition previously discussed under the title of splenomegaly with early hemorrhage, this disease consists of constant anemia, leucopenia, and persistent splenomegaly. Traditionally, it has been known as Banti's disease, but Banti's original description may or may not apply to a disease entity. The diagnostic criteria are persistent pallor and splenomegaly not associated with discoverable infection and unrelieved by medicinal treatment. It is important to rule out infection, especially in childhood, for this syndrome may be produced by a variety of diseases, such as tuberculosis of the spleen, and chronic meningococcemia with splenomegaly and *Streptococcus viridans* infection of the spleen. All of these have been found in association with anemia, leucopenia, and splenomegaly, and proved, unfortunately, only after splenectomy. Visceral sarcoid (of Boeck) has likewise been demonstrated in two instances.

The laboratory data include moderate anemia of the hypochromic microcytic type, constant leucopenia, poor regeneration of both leucocytes and erythrocytes, and often a somewhat lowered platelet level.

The complications of the disease are frequent secondary infection, and in the classical case, the development of cirrhosis of the liver, ascites, and terminal hematemesis.

Splenectomy has been advised for the relief of the anemia, leucopenia, and thrombocytopenia which occurs so frequently in the child with splenic anemia. It has been pointed out, particularly in the adult, that if the blood platelets are normal before operation, splenectomy is followed by a thrombocythemia which may lead to dangerous and even fatal intravascular thromboses. For such cases, the operation is contraindicated.

6. *Gaucher's Splenomegaly.*—In this condition, splenomegaly and hepatomegaly may be outstanding features; in fact, the largest spleens seen in childhood have been associated with this metabolic disturbance. A familial incidence is uncovered in about 20 per cent of the cases. In physical examination, one occa-

sionally finds pingueculae on the sclerae. These small fatty deposits may suggest the diagnosis. Generalized lymphadenopathy, though not to a marked degree, is found. Occasionally, the skin shows generalized brown pigmentation. Roentgenograms of the long bones may show skeletal extension of the disease. Where this is not present, confirmation of the diagnosis may be sought by biopsy, either of a lymph node or other affected tissue.

The laboratory data include a mild anemia of the hypochromic type and leucopenia; thrombocytopenia and developing aplastic anemia are found only in the advanced cases.

One of the complications is a marked enlargement of the abdomen, due to the increasing splenomegaly. The weight of this organ may become so burdensome and the drag on the stomach and diaphragm so constant that the patient suffers pain, indigestion, and increasing fatigue. In children, growth of the skeletal system and the development of bones and muscles may be hampered, so that the patient is far below the average for the age. Increasing skeletal involvement may lead to pathologic fractures of the bones. Where splenomegaly is not marked, this may be the first evidence of the disease.

TABLE I

SUMMARY OF RESULTS

Congenital hemolytic anemia 30	Unoperated, 6: 4 dead 2 unimproved Operated, 24: 2 dead 1 unimproved 21 recovered	Splenectomy most certainly indicated: As soon as diagnosis established Relieves hemolytic crises Avoids complications Restoration to normal health, growth, etc.
Splenic anemia 14	Unoperated, 3: 3 dead Operated, 11: 2 dead 6 improved 3 unimproved	Splenectomy indicated: For relief of anemia, leucopenia, and thrombopenia Better health, growth, etc.
Gaucher's splenomegaly 6	Unoperated, 0 Operated, 6: 4 improved 2 unimproved	Splenectomy indicated: For relief of mechanical burden due to tremendous splenomegaly ?Early operation may reduce possible spread
Thrombopenic purpura 40	Unoperated, 31: 23 recovered 6 unimproved 2 dead Operated, 9: 5 recovered 3 unimproved 1 dead	Splenectomy occasionally indicated: In persistent cases for relief from exsanguinating hemorrhage, or in child difficult to control, or after puberty in girls suffering from prolonged and severe menses
Splenomegaly with early hematemesis 18	Unoperated, 5: 3 dead 2 unimproved Operated, 13: 6 dead 3 improved slightly 4 recovered	Splenectomy questionably indicated: Removal of spleen should be accompanied by search for venous obstruction, ligation of varices, and omentopexy
Aplastic anemia 11	Unoperated, 7: 2 dead 3 recovered 2 unimproved Operated, 4: 2 improved 2 unimproved	Splenectomy questionably indicated: May result in remission or in less frequent need for transfusion

Splenectomy has been advised for the relief of the mechanical burden due to the tremendous enlargement of the organ. Occasionally, early operations may reduce the extension of the deposits of typical Gaucher's cells in the skeletal system.

7. *Congenital Hemolytic Anemia.*—This is the disease for which splenectomy is most beneficial in childhood. The operation is indicated as soon as the diagnosis can be established.

The diagnostic criteria consist of the presence of recurrent jaundice and anemia, usually occurring in crises, associated with high fever, abdominal pain, nausea, vomiting, and general weakness. During such crises, a severe anemia develops, the blood shows numerous reticulocytes, and the urine and stools contain large amounts of urobilinogen. The icterus index is markedly increased, and the van den Bergh test gives an indirect reaction with a great increase in bilirubin content of the blood. Even between hemolytic crises, the blood smears contain microcytic globular cells, and the erythrocytes are much more fragile than normal in hypotonic saline solutions. This is a valuable confirmatory test. Roentgenograms in children who have had the disease for several years show increased marrow activity as evidenced by wide bones with thin cortices and enlarged marrow spaces. This may be seen best in the x-rays of the hands and of the skull. Although a familial incidence should be sought, it occurred in only about one-third of the cases seen by us.

Complications in childhood are numerous. The recurrent anemia may be so severe that, in the very young patient, death may result from anoxemia and cardiac dilatation and heart failure. In the more chronic cases, chronic cardiac hypertrophy and dilatation often are found, and secondary decompensation and pneumonia may occur at any time, after a hemolytic crisis. Interference with growth and development and with normal activity often ensues. In the child, as well as in the adult, gallstones are found in some of the chronic cases.

Splenectomy is indicated as soon as the diagnosis has been substantiated, because the younger the patient, the more likely are the crises to be severe, and delay in operation may seriously handicap the patient. Transfusion should be given as needed, but to resort to frequent transfusions may increase the tendency to blood destruction and jaundice.

In response to splenectomy, there is an immediate improvement in the patient, particularly a rise in erythrocyte levels, diminution in blood destruction, freedom from jaundice, and often complete cessation of hemolytic crises. Occasionally, the blood platelets rise to a very high level within a week of splenectomy, and the danger of spontaneous intravascular thromboses exists. X-ray therapy at such times may reduce the platelet level. More recently, intravenous heparin has been advised to control this tendency to intravascular thrombosis.

To sum up the results of splenectomy in over 100 cases of splenomegaly which we have followed, reference may be made to Table I which details the numbers of patients with each type of splenomegaly, as well as the numbers subjected to splenectomy, and the results of this operation.

Academy News

In the Academy News of the September issue, a statement was made of Academy activities in relation to sending 'mercy ships' to bring refugee children from Great Britain, and their medical care in the United States. This statement included information up to August 16. As of September 25, no ships have been sent, and seemingly there is no immediate prospect of their being sent. The necessary legislation was enacted by Congress and signed by the President the latter part of August, but immunity has not been granted and the situation developing in England during the two weeks previous to the time of this note has seriously complicated the picture and delayed execution of the plan.

The response of the Academy to the requests of the Committee on Defense and Relief has been outstanding. Nearly forty volunteers have offered their services for the pediatric medical work on the ships as well as sufficient volunteers for surgery, and their names are on file with the Committee. So far, a few undesignated children have arrived on British ships, and their examination and medical care have been provided for by the committee under Dr. McIntosh in New York. As it seemed likely that some ships would land on the Brooklyn shore of New York Harbor, a similar unit has been organized by Dr. Carl Laws of Brooklyn. Without exception, every Academy member asked to set up the local medical care responded immediately, accepting the responsibility.

News and Notes

Under the rules laid down by the American Academy of Pediatrics, its new educational-to-the-public film "When Bobby Goes to School" may be exhibited to the public by any licensed physician in the United States. All that is required is that he obtain endorsement by any officer of his county medical society. Endorsement blanks for this purpose may be obtained on application to the distributor, Mead Johnson & Company, Evansville, Ind. Such endorsement, however, is not required for showings by licensed physicians to medical groups for the purpose of familiarizing them with the message of the film.

"When Bobby Goes to School" is a 16-mm. sound film, free from advertising, dealing with the health appraisal of the school child, and may be borrowed without charge or obligation on application to Mead Johnson & Company.

Dr. John A. Toomey has been promoted from associate professor of pediatrics in the School of Medicine of Western Reserve University to professor of clinical pediatrics and contagious diseases.